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example and precept

The association of cigarette smoking with lung cancer is now well established. The youth who smokes twenty-five cigarettes a day is fifty times as likely as is his nonsmoking brother to have cancer of the lung after 45 years of age. Moreover, the mortality rate from lung cancer is lower in men who give up smoking than in continuing smokers. It is, therefore, no longer admissible to condone smoking on the assumption that the harm has already been done and that stopping would be futile.

The duty of the physician is clear—to weigh the evidence, laboratory and statistical, concerning the relationship between cigarette smoking and lung cancer, and, if he finds cigarettes indicted, to exhort his younger patients not to start and his older patients to stop or moderate their smoking; and, above all, if he is himself a cigarette smoker, to stop smoking, showing the patient that it can be done. Then he no longer need say unconvincingly "Not as I do but as I say."

A laudable example was set by the vote of the British Medical Association to refrain from smoking at the sessions of their Annual Convention at Brighton, July 5-13, 1956.

Cover—

Adapted from EAST RIVER TUG by Dong Kingman (1955). Water color. Courtesy of the artist.

Dong Kingman (born 1911) is represented in the permanent collections of the Metropolitan Museum, Whitney Museum, American Academy of Arts and Letters, Museum of Modern Art, Brooklyn Museum, Boston Museum, Art Institute of Chicago, San Francisco Museum, De Young Museum, Mills College, Universities of Nebraska and Wisconsin, Springfield, Illinois, Art Association, Davenport Municipal Art Gallery, Fine Arts Gallery of San Diego, Bloomington Art Association, Toledo Museum, and many other art galleries and museums throughout the United States.

He has won two Guggenheim Fellowships, the $500 award at the Metropolitan Museum in 1953, both the Philadelphia Watercolor Prize and the Pennell Medal at the Pennsylvania Academy, three prizes at American Watercolor Society Annuals, the Audubon Gold Medal of Honor and an award at the Chicago Art Institute.

As an important representative of contemporary American artists, Dong Kingman made a recent round-the-world trip sponsored by the State Department as part of an intercultural exchange program.

"He looks at New York as no one else does—as no other painter, writer, composer, photographer looks at it, —"

—William Saroyan in *The Eye and Hand of Dong Kingman*

Particulate air pollutants—automobile exhaust, coal and oil smoke, dust, smog, etc. —are coconspirators with cigarette smoke in association with lung cancer.

NEWSLETTER

SEPTEMBER, 1956

The Third National Cancer Conference in Detroit, June 4-6, seemed to win the enthusiastic approval of the 1700 physicians and scientists who attended. Its success can be attributed to one simple formula: Those who planned it determined to make it as newsy as possible. The material was fresh, forthright, and provocative. Sessions were well attended. A large delegation of science writers carried the cream of the proceedings to the general public. It may take years to evaluate the true significance of some of the work presented at the Conference. The following is a general idea of some of the subject matter and the people who presented it.

VIRUSES

Nobelist Wendell M. Stanley (U. of Calif.) blessed the virus theory of cancer etiology. Concluding a scholarly review of the mounting evidence, he stated: "The experimental evidence now available is consistent with the idea that viruses are the etiological agents of most, if not all, cancer, including cancer in man. Acceptance of this idea as a working hypothesis is urged because it will result in the doing of experiments that might otherwise be left undone, experiments that could result in the solving of this great problem. The past few years have seen the development of important new knowledge and of especially powerful new tools, and if we take full advantage of these we could easily tip the scale towards the solution of the cancer problem." He paid tribute to Duran-Reynals, Oberling, and a few others who long ago speculated, on substantial evidence, that viruses caused cancer and who were abused for their boldness. He acknowledged the considerable contributions of Borrel, Rous, Andrewes, Gey, Bittner, Lwoff, and many others, including Fraenkel-Conrat and Williams in his own laboratory, for supplying important pieces in the virus jigsaw puzzle. "Although Rous, Andrewes, Gey, Duran-Reynals, Oberling and Guerin and a few others have provided eloquent and persuasive testimony for the acceptance of viruses as the etiological agents of cancer, the majority of the cancer investigators have tended to disregard this testimony," he

said. "Evidence for the virus etiology of cancer has come from so many different laboratories and has been of such good quality and quantity that I find it very difficult to understand why so many investigators have continued to have such a firm blind spot with respect to the virus causation of cancer. However, during the past few years there does seem to have been a definite change in the attitude . . . In 1952 I stated that 'Twenty years ago the relationship between viruses and cancer was scarcely mentioned and when it was, one had to speak softly. Today large and well attended conferences are held on this same subject and virus-induced tumors in animals and plants are accepted generally.' The trend has certainly been in the right direction, but I must say that I continue to be amazed at the willingness of so many investigators to accept viruses as etiological agents for animal cancers and their unwillingness to consider them of etiological importance in cancers of man. Cancer is a biological and not a theological problem . . . Basic biological phenomena generally do not differ strikingly as one goes from one species to another . . . Cancer is basically a problem in growth, and there is no reason to believe that the growth of most human cells is different basically from the growth of most animal cells."

Joseph W. Beard (Duke) advanced the opinion that we shall know within a few years whether or not human leukemia is virus caused. With D. Gordon Sharp and Dorothy Beard, he presented evidence that the virus of chicken leukosis has adenosine triphosphatase activity.

Ludwik Gross (Bronx V. A. Hospital) reported on experiments in which some mice, injected with the leukemia agent, developed unilateral or bilateral parotid tumors, and others developed subcutaneous sarcomatous tumors. Filtrates from the parotid and sarcomatous tumors, inoculated into newborn mice, produced leukemia as well as parotid or subcutaneous tumors. Among the possible explanations considered by Gross are: (1) a single oncogenic agent induces different types of tumors or generalized leukemia; or (2) leukemia and certain tumors contain several distinct oncogenic agents -- one at a time becoming pathogenic. He speculated that many viruses capable of causing tumors may exist, lying dormant until age or an agent sets them off.

LEUKEMIA AND LYMPHOMA

Steven O. Schwartz (Hektoen Institute and Cook

County Hospital) cited a series of provocative experiments that challenged conventional concepts of virus-species specificity and attracted attention to nerve as a common habitat for leukemogenic viruses. Filtrates from the brains of human leukemic patients injected into young adult susceptible mice accelerated the appearance of leukemia in the animals -- the leukemia appeared in a few weeks instead of many months following a single small inoculation. Guinea-pig serum, agglutinating both human and mouse leukemic cells, showed a cross reaction between the two species; and a specific agglutinin, prepared in rabbits for both leukemic humans and leukemic mice, was adsorbed selectively by the leukemic red cells of either species. Schwartz read these results as implying: (1) a viable agent is responsible for leukemia in both mouse and human; (2) immunological similarities exist between the leukemias of the two species; (3) leukemia, in its morphological manifestation, represents the host response of the pluripotential mesenchymal tissues to an exogenous agent (probably virus or virus-like); and (4) the sites of greatest morphological response (tumor tissue, lymph nodes, etc.) are the poorest, while the sites of least morphological response (brain) are the richest, sources of the inducing agent. In mouse-to-mouse experiments, the Schwartz group produced leukemia in susceptible mice with brain filtrates in an average of four to five weeks; and they recovered the agent after ten passages in the brains of resistant mice, which themselves did not develop the disease.

Arthur Kirschbaum (Baylor), one of the most highly productive investigators of the fundamentals of leukemia, showed that genetic resistance to the disease can be overcome with common carcinogens -- roentgen rays, estrogens, or methylcholanthrene. Given early to some resistant strains, the leukemogens worked. Oddly enough, however, the same leukemogens were ineffective when given to some highly susceptible strains. Moreover, additive effects were obtained when two or more of the agents were given to strains responsive to single agents -- a strong suggestion that the various leukemogens may pursue a common pathway. Kirschbaum, reviewing his own and others' results, cited as among the factors involved in mouse leukemia: (1) genes -- which exert their influence on the target tissue (various strains are affected differently by the same carcinogen); (2) the thymus -- its removal reduces susceptibility to spontaneous

and induced leukemia; (3) steroid hormones -- estrogen alone may be leukemogenic or act additively with roentgen rays; male hormone nullifies estrogens and depresses the effect of carcinogens; cortisone delays spontaneous and induced leukemia; (4) aging -- the younger the animal the more susceptible it is to leukemogens; the longer the strain's life expectancy, the greater the delay in the appearance of leukemia (hybrids live longer than inbred strains and develop leukemia later); and (5) a maternal resistance factor -- when high leukemia strains are foster nursed by low leukemic-strain mice, leukemia incidence is reduced and the disease delayed.

William Dameshek (New England Medical Center) in a lucid and thoughtful lecture on the bone marrow "organ" (in total volume about the size of the liver) cited proliferative overgrowth of one or several marrow elements and irreversibility in polycythemia vera as resembling a malignant disease, while its lengthy (ten- to twenty-year) course puts it in a more benign category. He said that in about eight of every ten idiopathic cases there is a history of pronounced chemical exposure, usually to aromatic solvents (benzol, toluol, xylol, or carbon tetrachloride). He noted that polycythemia cases have been described in association with pituitary and hypothalamic disorders and at times with hypernephroma and Cushing's syndrome, and he recalled that "stressed," highly dynamic individuals have borderline values for red-cell, white-cell, and platelet counts -- further evidence for the suspicion that neuroendocrine factors may be involved. He concluded: "One must learn to look at these myeloproliferative syndromes not as static, categorically well-defined entities, but rather as dynamic, ill-defined conditions, perhaps reactive to certain stimuli, and perhaps to be attacked by less 'brutal'and destructive methods than we now possess. Were one to find fundamental causative mechanisms, perhaps of a humoral nature, their conquest might be closer at hand."

R. Wayne Rundles (Duke) asserted that "reasonably rapid progress" is being made toward eventual control of multiple myeloma. In a series of 124 cases studied over eight years, one third were not helped (because of delayed diagnosis and treatment), one third received moderate benefit, and one third received great help from cortical steroids and urethane. He added that the Chester Beatty compound -- 1248 -- shows promise.

Charles C. Congdon (Oak Ridge) pointed out that partial body shielding markedly reduces leukemia, a latent effect of radiation, just as it reduces immediate lethal effects. He reported that so far the only isotope to produce leukemia in animals is P^{32}. Intravenous doses of bone marrow after irradiation did not reduce the incidence of leukemia, although it did extend survival time to three or four times that seen in nontreated animals.

Michael B. Shimkin (N.C.I.) reported that an analysis of several studies indicated that the leukemia death rate has increased sixfold (from 10 to 63 per million) over the last fifty years and 20 per cent between 1949 and 1953. Significantly higher than the national average were rates for Minnesota, New York, and California. Higher income groups seemed to be among the more susceptible. Poor reporting practices, however, probably account for much of the "rise" in incidence.

Frederick A. Coller and C. Thomas Flotte (U. of Mich.) declared that lymphomas of the gastrointestinal tract are an important, if not common, type of neoplasm. Some remain localized for variable periods before becoming systemic in nature. They sometimes closely resemble carcinoma in symptomatology, roentgenological, and gross appearance and must be differentiated because resection, with or without subsequent roentgen-ray therapy, may give long-term survival.

A. C. Upton (Oak Ridge) and Jacob Furth (Children's Cancer Research Foundation) listed these as factors influencing leukemia:

Genetic. These are debatable. While identical twins frequently develop leukemia, the disease in only one twin points to other factors. Familial and racial differences may be similarly interpreted.

Immunogenetic. These factors, influencing transplantation success and rate of growth, may be modified by cortisone or roentgen rays.

Age. The younger the host the easier it is to induce leukemia. And the older the mother or the foster mother, the lower the incidence -- evidence of a humoral resistance factor developing with age.

Diet. Caloric restriction cuts the incidence of leukemia too.

Endocrine. Leukemia is more common in human males and in mouse females (of most strains). In some strains of

mice the disease has been influenced by gonadal, pituitary, cortical, and thyroid hormones.

Thymus. Irradiation of the thymus in children may increase leukemia -- but not in mice. An intact thymus is essential to the development of some mouse leukemias.

Marrow. Injected isologous, nonirradiated marrow inhibits radiation-induced leukemia in some mice. So does shielding marrow and spleen during irradiation. And susceptibility or resistance can be conferred to some degree by injecting young adults with marrow from the desired strain.

LUNG

Oscar Auerbach (East Orange V.A. Hospital) issued a progress report that served to strengthen the suspicion that cigarette smoking may lead to cancer. (Only an industry spokesman in New York rebutted the findings as "proving nothing.") He has examined at autopsy an average of 208 sections of the tracheobronchial trees of 117 men, thirty-four of whom died of lung cancer. (All thirty-four were smokers.) He found degrees of basal-cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ closely correlated with the smoking history of those who died of lung cancer and of those who died of other causes. Eye-opening was the fact that carcinoma in situ peppered the lungs of all classes (indicating, particularly in nonsmokers, the existence of etiological agents other than cigarette smoking). The findings -- of multiple foci of bronchogenic carcinoma -- may explain the difficulty of curing lung cancer by surgery.

Robert E. Stowell (U. of Kansas) viewed as not very valuable present cytological techniques for the detection of lung cancer. He pointed out that, while positive reports frequently are 90 to 95 per cent or more accurate, false negatives for persons later found to have the disease have been around 50 per cent in some series. The big needs, he said, are a convenient method of obtaining cell samples, better methods of preparing and examining specimens, and improved training of technicians and pathologists.

L. Henry Garland (Stanford) stated that roentgen-ray diagnosis could be improved by a more thorough examination of suspect adults, dual interpretation of the roentgenograms, and radiologist-physician consultation.

Leo G. Rigler (City of Hope Hosp.) said failure to diagnose lung cancer is largely due to poor interpretation of

roentgenograms and the cursory procedure undertaken. He emphasized the need for reviewing old roentgenograms and paying particular attention to minor changes seen in new pictures.

William J. Tuddenham (U. of Pa.), while agreeing that interpretation of roentgenograms is important, called for better radiographic techniques. "If an image were clearly enough defined and sufficiently impressive, it is unlikely that it would escape detection in even the most cursory study," he said. "Ideally, we should like to develop a technique which would make the image of a lung cancer so obvious that it could not be overlooked." Granting that this idea might be impossible to achieve, he held that the best approach at present is in supervoltage roentgenography, although body-section technique serves much the same purpose. He reviewed the experience of investigators reading supervoltage roentgenograms and found it imperfect but promising as things now stand.

C. C. Little (Bar Harbor) cautioned against seizing upon simple explanations of cancer's etiology with any sense of completeness or satisfaction. He said this is particularly true of tumors such as bronchogenic carcinoma that are affected by age, sex, degree of accuracy of diagnosis, geographical location and possibly previous infection, irradiation, and air pollutants.

Richard H. Overholt (New England Deaconess) reported on the survival of 6009 lung-cancer patients, most of them diagnosed between 1942 and 1950. Of those with apparently localized lesions, 15 per cent survived five years; of those with lesions extending to mediastinal lymphatics or with gross invasion of other structures, only 5 per cent survived five years; with distant extension, 0.3 per cent survived five years. Although 5 to 8 per cent of all patients survived five years, 19 to 28 per cent of all who had pulmonary resections survived five years, and 29 to 38 per cent resected for localized lesions lived five years. He urged immediate surgery for patients showing definitely suspicious shadows. "Time cannot be lost waiting for x-ray change," he declared. "The x-ray evidence must be evaluated on the basis of the immediate study. If the shadow is to grow, so must the cancer. From the beginning, cases can be evaluated from the standpoint of hazards -- the risk of the cancer potential of the x-ray shadow against the risk of surgical exploration and total biopsy. With full and intelligent application of

known methods of detection and treatment, more than 50 of 100 cancer victims can be saved."

Vincent P. Collins (Baylor) reported on supervoltage roentgen-ray treatment of lung cancer. "With available supervoltage equipment," he said, "it is possible to treat cancer of the lung as simply as a cancer of the skin and even in a single treatment. This technical advance, however, is limited by the fact that, whereas skin cancer is accessible to early observation in treatment while localized, lung cancer tends to grow and spread silently for a long time before its presence is detected." He suggested supervoltage therapy for palliative purposes as well as for cure.

Morton L. Levin (N. Y. State Dept. of Health) proposed a study to determine the benefits of giving up cigarette smoking. He suggested that men between 45 and 69, now regular smokers, be enrolled. They would agree to give up or not give up smoking for several years and their fate would be followed.

William E. Adams (U. of Chicago) reported that in dogs it was possible to reduce functional lung capacity to one upper lobe (or 15 per cent); but this doubles pulmonary tension (from 32/5 to 64/8 mm. mercury). Only four of thirteen dogs in these experiments survived, the rest dying of cardiac failure. The results indicate that pulmonary hypertension after resection may be a factor in postoperative death in lung cancer. He suggested a thorough study of the cardiovascular reserve in elderly people prior to operation.

FEMALE GENITAL TRACT

In several papers combining results of both animal and clinical studies, John and Ruth Graham (Harvard and Mass. General) related rapid progress toward immunological treatment of cervical cancer. Previously they noted that the patient's ability to produce antibodies against her own tumor held prognostic significance -- the higher the antibody titer the better the prospects of cure. More recently they have found that, by injecting antigens intradermally and then irradiating the injected area, they were able to raise the antibody titer against the specific antigen. This procedure has been tried against four kinds of tumor in thirty-odd patients, using a nucleoprotein fraction of the tumor as the antigen. While the cytological results indicate

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Keeping up

Origins of the Cancer Cell

Normal cells become cancer cells through irreversible injury to their respiration by the remote causes of cancer—tar, radiation, arsenic, pressure, urethane. This respiratory injury, which is the one common cause of cancer, leads to death of those cells that cannot compensate the respiratory-energy loss by energy derived from fermentation. Those cells that do compensate by successfully substituting the morphologically inferior fermentation energy for the respiration energy of the highly differentiated body cells are changed into undifferentiated cells, like yeast, and grow and multiply wildly—the cancer cells. Normal liver and kidney cells obtain 100 times as much energy from respiration as from fermentation; the ascites-cancer cells of the mouse obtain approximately equal amounts of energy from fermentation and respiration. Chronic intermittent oxygen deficiency probably plays a greater part in the formation of cancer than does the chronic administration of respiratory poisons. Frequent small doses of respiratory poisons are more apt to cause cancer than a single large dose that may kill the cells rather than convert them into cancer cells. Carcinogenesis by irradiation is simply a destruction of respiration by elimination of the respiring cell grana (mitochondrial elements). The respiring grana are no longer considered to be mere insoluble cell particles but biochemically and genetically autonomous organisms with important roles in heredity and in the genesis of neoplasia. The latent period of cancer is the interval between the respiratory injury and the time at which the compensating increase in fermentation occurs. This interval is especially long in man. It may be as long as several decades in the cases in which the time of respiratory damage is known—arsenic cancer and irradiation cancer. In sleeping cancer cells, fermentation, after respiratory injury, has increased sufficiently to initiate dedifferentiation but not enough to compensate fully for the respiratory defect. Such latent, silent cells are found in the prostate, lung, kidney, and stomach of many elderly asymptomatic persons. The author concludes from his energy studies that these sleeping cells could be killed more readily than growing cancer cells and suggests that these cells in precancerous skin are the most suitable test objects for finding effective anticancer agents.

Warburg, O.: On the origin of cancer cells. Science 123: 309-314, Feb. 24, 1956.

Cytology in Lung Cancer

From a biopsy specimen obtained at bronchoscopy, a histological diagnosis can be made in about 50 per cent of pulmonary-cancer cases. In order to determine the value of cytological as compared to biopsy examination in diagnosis of lung cancer, 580 patients were studied. Neoplastic cells were found at cytological sputum examination of 70.7 per cent of the group of histologically confirmed lung cancer; whereas cytological examination of bronchial secretions in the same group gave correct positives in 79.5 per cent. Cytological sputum examination increased the number of preoperative microscopic pulmonary diagnoses by 26.7 per cent.

with Cancer

and cytological examination of bronchial secretions increased the number of microscopic lung-cancer diagnoses by 20 per cent compared with results obtained by examination of bronchoscopic biopsy specimens. Cytological diagnoses should be confirmed by biopsy when possible. Although the cytological examination of sputum and bronchial secretions is not entirely perfect, it is a valuable supplement to other diagnostic methods. It has the advantage of not contraindicating other diagnostic methods and of often permitting a diagnosis while the pulmonary cancer is still in an early and successfully operative stage.

Hjelt, L.: Cytodiagnosis in pulmonary cancer; the significance of a cytological examination of sputum and bronchial secretion in the diagnosis of pulmonary cancer. Ann. chir. gynaec. Fenn. 40: (suppl. 3): 1-68, 1953.

Cancer of the Cervical Stump

With the object of reducing the delay in recognizing and treating carcinoma of the cervical stump, 150 histologically proved invasive cases were analyzed. This group represented 6.83 per cent of the total 2195 patients with carcinoma of the cervix investigated. Vaginal bleeding and discharge were the most frequent symptoms in cervical-stump cases. Thirty (20 per cent) of the 150 had "coincident" carcinoma of the stump (occurred within two years of the original hysterectomy and may be presumed to have been present at the time of the operation). The physician was wholly to blame for the delay in treatment in forty cases, and contributed to the delay in thirty-eight more, a total of 52 per cent of the group. The five-year survival in this group of cases of true and "coincident" cancer of the cervical stump was 36.6 per cent. Whenever hysterectomy by the abdominal route is contemplated, complete hysterectomy is the operation of choice. In those rare cases in which complete hysterectomy is not advisable, the cervix should be properly treated, and careful cytological studies made, preferably by circular biopsy and endocervical resection; and the patient must be carefully examined at frequent intervals. The most frequent cause for patient delay was that the bleeding was so meager as to be thought unimportant. The most frequent factors in the physician's delay were failure to examine the patient, to recognize the cervical lesion, and to make a cytological study and biopsy. With proper inspection of the cervix, careful cytological study, and adequate treatment for benign disease of the cervix, few stumps would remain to become cancerous.

Hahn, G. A.: Carcinoma of the cervical stump with special reference to the causes of delay in therapy: observations from data of the Philadelphia Committee for the Study of Pelvic Cancer. Am. J. Obst. & Gynec. 71: 413-420, Feb., 1956.

Radiotherapy of Cancer

After half a century of empiricism, radiation therapy has become a science based on physics, radiobiology, and clinical experience. Radiation and surgery are the only available weapons for the cure of cancer. Chemotherapy is confined to palliation. Nuclear physics continues to make available new sources of radiation, so that now it is possible to deliver lethal amounts of ionizing energy anywhere in the body regardless of depth. The wide spectrum of

sources includes: low-energy roentgen rays (45 kv.) used in skin cancer; deep roentgen rays (200 to 250 kv.); million volt machines (1 to 2 Mev); Co^{60} teletherapy (3 Mev equivalent); ultrahard roentgen rays produced by betatron or linear accelerators, and many gamma-ray (roentgen-ray) or beta-ray (electron) isotope emitters. These various sources of wave or corpuscular radiation produce biological changes responsible for damage to living cells through the process of ionization and differ only quantitatively. The basis of radiotherapy is the relative radiosensitivity of cancer and surrounding normal tissues. Ideally the ionizing agent would affect only the tumor cells. This is almost achieved by the beta-ray emitters I^{131}, P^{32}, and Au^{198}. Tumors sensitive to these isotopes can be heavily irradiated without appreciable damage to adjacent structures. Certain thyroid tumors, leukemia, and reticuloendothelial tumors are treated in this manner successfully. The difficulties are the spottiness of uptake with resultant overirradiated and underirradiated areas and the possibility of damage to very sensitive structures, such as bone marrow. Eradication of tumors by irradiation is possible only when their cells are more radiosensitive than are those of the supporting structures. Tumors that are as radioresistant as the adjacent healthy tissues, such as neurogenic sarcomas and melanomas, are not to be treated by irradiation. Radiosensitivity is not necessarily radiocurability. Tumors such as the lymphomas are very radiosensitive but rarely radiocurable because they either generalize quickly or are generalized when first seen. Keratinizing squamous-cell carcinomas, on the other hand, require very high doses of radiation, approaching the tolerance of supporting structures. If the lesions are at localized and accessible sites, however, such as skin, lip, oral cavity, or vagina, very high doses can be given to small volumes of tissue with possible recovery. Deeply situated squamous-cell carcinomas, such as those of the esophagus, can be irradiated successfully by cross-firing and rotation techniques. However, as the disease becomes more extensive, the volume to be irradiated is increased, and the tumor dose must be reduced as the tolerance of the tissues decreases. Radiation is then no longer curative, only palliative.

When both radiation and surgery are used, it may be either separately or combined. When the tumor is radioresistant, as the neurogenic sarcomas and adenomas of the gastrointestinal tract, surgery is the sole method of treatment; when the tumor is extremely radiosensitive, as lymphomas, radiation is the treatment of choice. In the case of tumors amenable to both radiation and surgery, the choice of therapy is made by the surgeon-radiotherapist team based on mutual experience with similar tumors. For example, in early tumors of the vocal cord, laryngectomy is highly curative and so is radiotherapy. If there is residual or recurrent disease, a laryngectomy can still be performed, and the patient has lost neither his chance for survival nor his chance for preservation of speech function. The combination of surgery and irradiation increases survival rates in tumors of the paranasal sinuses, extrinsic larynx, and oral cavity. Sequences of combined therapy are decided by the experienced surgeon-radiotherapist team. Surgery and radiation are used complementarily, one to treat the primary lesion and the other the metastatic lymph nodes, as in cancer of the tongue treated by radium implants and metastatic lesions of the nodes of the neck treated by radical neck dissection. In breast cancer, surgery removes the primary lesion and the axillary nodes, and radiation treats the apical axillary, supraclavicular, mediastinal, and internal mammary nodes, all inaccessible to moderately radical surgery. Ionizing radiation is highly toxic and damaging and should never be used without a specific purpose. Radiation necrosis superimposed on growing cancer is more painful than cancer alone. The greatest kindness to the patient is not always to employ aggressive therapy by the indiscriminate use of a highly damaging agent.

Fletcher, G. H.: Radiotherapy in the management of the cancer patient. Postgrad. Med. 17: 490-497, June, 1955.

at a glance . . .

one-minute abstracts of the current literature on cancer . . .

Cancer of the Lung—Diagnosis

Roentgen-ray examination, either by simple photofluorography or a full-sized posteroanterior view of the chest, is an excellent method for detecting disease of the lung, including carcinoma. To identify the lung disease as carcinoma requires chest films made in a variety of positions and in both respiratory phases, planigraphy, and bronchography, which often make the diagnosis definite and justify urging operation. Chances for success of the curative procedures—pneumonectomy and lobectomy—depend largely on the early detection and rapid identification of lung cancer. Opportunity for detection of lung cancer in the curative stage is greater than for cancers of most other sites owing to its characteristically slow development, some lung cancers remaining asymptomatic and localized for a number of years. Signs appear on the roentgenogram nine months and longer before the patient is aware of first symptoms. Repeated roentgenological examinations usually give evidence of the disease process in its very earliest, or smallest, stages. The numerous chest surveys carried out in this country have not been strikingly successful in finding early cancer of the lung. Insufficient attention has been given to minor details, which often are quite apparent in retrospect after the lesion has become obvious. When suspicion arises from the roentgenogram, bronchoscopy or examination of the sputum usually will confirm the diagnosis immediately. In only two of 400 cases were symptoms present without roentgenographic evidence of disease in the lung. The most important method of making an unequivocal diagnosis is the microscopic examination of tissue removed through the bronchoscope, by percutaneous biopsy, or by open thoracotomy. Cytological demonstration of cancer cells in the sputum or bronchial aspirations is another excellent method for positive identification. Exploratory thoracotomy should be withheld until all other diagnostic methods have been exhausted.

Rigler, L. G.: X-ray diagnosis of cancer of the lung. Postgrad. Med. 18: 361-373, Nov., 1955.

Cigarettes and Lung Cancer

Cigarette smoking is probably the principal cause of the increase in lung cancer that has been noted in many parts of the world during the past two decades. In patients with squamous or anaplastic carcinoma of the lung, but less so with adenocarcinoma, there is a relationship with cigarette smoking. The recent tremendous increase has been in the epidermoid or anaplastic carcinoma of the lung.

There are other etiological factors besides smoking. Lung cancer is rare in population groups that do not smoke, as in Iceland before 1945. The risk of developing lung cancer rises in proportion to the amount of tobacco consumed. This risk has been reported to be ten- to fifty-fold over the nonsmoker. Only 15 per cent of lung cancers occur in nonsmokers. Ninety per cent of epidermoid lung cancers in men are associated with tobacco smoking, and in the absence of smoking these 90 per cent would not occur. Risk of developing lung cancer is not influenced by residence in an urban or a farm area. Cancer of the larynx, the oral cavity, and probably the esophagus are also closely associated with tobacco consumption. Smoking with inhaling is more apt to cause lung cancer than without inhaling. The latent period for lung cancer is twenty to thirty years. As the female population approaches this thirty-year smoking experience, we can expect a sharp rise in the incidence of lung cancer in the female, approaching that in the male. It is not probable that cigarette paper is the guilty carcinogen. It is recommended that smokers have a chest roentgenogram twice a year in order to detect lung cancer in an early, operable, and curable stage.

Coffin, G. J. (Moderator); Duryee, H. C.; Maier, H. C.; Pardee, H. E. B., and Wynder, E. L.: The effects of tobacco smoking. [Panel Meeting] Bull. New York Acad. Med. 32: 133-156, Feb., 1956.

Giving up Smoking

Since the discussions on a relationship between lung cancer and smoking, patients who have smoked for years sometimes ask what the effect of giving up smoking will be on their life expectancy. In other words, is the damage done and should they therefore continue to smoke, or is it a case of "never too late to mend"? From a study by the British investigators, Doll and Hill, of 1357 hospital patients with lung cancer and a control group of hospital patients of the same size, reported in 1952, it was estimated that the risk of developing lung cancer for a man who continued to smoke was approximately one and a half times as great as that for a man who had stopped for between one and ten years, and four times as great as that for a man who had stopped for ten years or longer. The calculation does not take into account differences in the numbers of cigarettes smoked a day, but, since a greater proportion of men who had given up smoking had been heavy smokers than of men who continued to smoke, this cannot be responsible for the difference between the estimated risks but must, rather, have minimized it. In a further inquiry Hill and Doll have been observing some 40,000 men and women doctors who provided information about their smoking habits at the end of 1951. Their results suggest that those smokers who ceased smoking by the end of 1951 are dying of lung cancer at a lower rate than those smokers who continued to smoke. A similar result is indicated by evidence obtained by Hammond and Horn in the United States. It is therefore reasonable to hope that a smoker who gives up his habit substantially reduces his risk of developing lung cancer.

Anon.: Giving up Smoking. [Editorial.] Brit. M. J. 1: 504-505, March 3, 1956.

Bronchogenic Carcinoma

Exact diagnosis of bronchogenic carcinoma can be made in only a limited number of cases; an exploratory thoracotomy is often required. Adequate preoperative studies are of value, however, in supplying information to aid in making the diagnosis at the time of thoracotomy. Preoperative studies include bronchoscopy with bronchoscopic biopsy, cytological examinations of sputum and bronchoscopic aspirations, roentgenographic examination of the chest, and biopsy of lymph-node metastases. The physicians using these methods must prove the absence of carcinoma or resort to thoracotomy. Bronchoscopy with biopsy yields positive diagnosis in but 20 to 25 per cent of cases. Early, small, and peripheral lesions will be missed by this method. Cytological studies add a limited number of positive diagnoses. The frequent cytological report "suggestive of malignancy" is not conclu-

sive but helpful. Roentgen-ray examination of the chest can establish a nearly conclusive diagnosis of bronchogenic carcinoma, but seldom in an early stage, and most commonly when some disastrous secondary effect, such as diaphragmatic paralysis or rib erosion, has occurred. At operation, accurate diagnosis and determination of the need or the extent of resection are often difficult, and results of the preoperative studies are of great value to the surgeon. Roentgenological findings highly suggestive of cancer, a sputum negative for tubercle bacilli, sputum or bronchoscopic aspirate "suggestive of malignancy," and a negative tuberculin test in a patient with good lung function are highly suggestive of cancer and fully justify pneumonectomy for a lesion otherwise undiagnosable.

Moulder, P. V.: Diagnosis of bronchogenic carcinoma. S. Clin. North America 36: 23-34, Feb., 1956.

Bronchial Histology and Smoking

Occurrence of basal-cell hyperplasia, stratification, and squamous metaplasia of the tracheobronchial epithelium, as revealed at operation or autopsy, was correlated with histories of smoking in fourteen cases of lung cancer and in twenty-seven patients without cancer or other clinical disease of the lung. Eight of these twenty-seven were nonsmokers, fourteen smoked one to two packs of cigarettes a day (light to moderate), and five smoked more than two packs a day (heavy). All of the fourteen patients with lung cancer were heavy smokers. Basal-cell hyperplasia was present to a greater degree in smokers than in nonsmokers. Stratification and squamous metaplasia were present to a slightly greater degree in smokers. It is suggested that further studies should include a greater number of patients; that women, children, and adolescents should be included; and that the influence of age and sex be evaluated.

Auerbach, O.; Petrick, T. G.; Stout, A. P.; Statsinger, A. L.; Muehsam, G. E.; Forman, J. B., and Gere, J. B.: The anatomical approach to the study of smoking and bronchogenic carcinoma: a preliminary report of forty-one cases. Cancer 9: 76-83, Jan.-Feb., 1956.

Tobacco and Lung Cancer

The mortality rate in England and Wales from lung cancer in 1955 was nearly thirteen times that in 1930 for men and five times that for women. This sex difference is an indication that the great increase in the incidence of lung cancer is not accounted for by better diagnosis. The accumulated evidence today is such as to denote a cause-and-effect relationship between cigarette smoking and cancer of the lung. The risk of dying from lung cancer is directly proportional to the amount smoked. There is no evidence of any "threshold" amount below which there is no added risk whatever. Approximately 9 per cent of men aged 25 years who smoke 25 to 50 cigarettes a day may be expected to die of lung cancer before they reach the age of 75—that is, one man in eleven. Published data indicate that there is an advantage to the heavy smoker in stopping smoking. Inhaling the smoke did not increase the risk. The risk in London is now twice that in the rural districts, but we should know the difference between urban and rural smoking habits twenty to thirty years ago to evaluate the etiological effect of city factors. The even greater male:female ratio of incidence in the large towns indicates that smoke in the atmosphere is an unimportant etiological factor, for, if it were important, a diminished rather than an increased sex disparity would be expected. Exhaust gas from petrol-engined vehicles contains the carcinogen 3,4-benzpyrene, but there is no evidence of increased incidence of lung cancer in road transport drivers, garage workers, or policemen.

Hill, A. B., and Doll, R.: Lung cancer and tobacco. Brit. M. J. 1: 1160-1163, May 19, 1956.

Bronchogenic Carcinoma in Persons Less Than 40 Years of Age

The findings at the Mayo Clinic in fifty-one patients less than 40 years of age in whom the diagnosis of primary bronchogenic carcinoma had been made in the years 1943 through 1954 are presented. The ratio of thirty-nine men to twelve

women (3.25:1) was appreciably lower than that reported for bronchogenic carcinoma in all ages, which varies from 5:1 to 10:1. Two patients were entirely asymptomatic. In the remaining forty-nine, the duration of symptoms before the diagnosis was established varied from two weeks to twelve months, the average being four and three-tenths months. Of forty-three patients whose symptoms were referable to the respiratory tract, cough and hemoptysis were the most frequent symptoms. Sixteen patients (31 per cent) gave evidence of inoperability by reason of distant or local spread on the basis of symptoms alone. The diagnosis was established by bronchoscopic visualization and biopsy of the lesion in twenty-one of thirty-two patients. In ten patients the diagnosis of primary bronchogenic carcinoma was made on the basis of clinical and roentgenographic findings and on histological examination of tissue removed at biopsy from distant metastatic foci. In nine patients the diagnosis was proved by the finding of malignant cells on cytological examination of sputum or bronchial secretions; in eight the diagnosis was established at surgical exploration of the thorax; and, in the remaining three, at autopsy. Bronchogenic carcinoma is a more rapidly fatal disease in patients of this age than in older persons. The chances of cure or even long survival are small and are practically nonexistent when metastasis to hilar lymph nodes has occurred. With the possible exception of squamous-cell lesions, which are infrequent in men and rare in women less than 40 years of age, the cell type does not appear to have prognostic significance in bronchogenic carcinoma in this age group.

Neuman, H. W.; Ellis, F. H., Jr., and McDonald, J. R.: Bronchogenic carcinoma in persons under forty years of age. New England J. Med. 254: 502-506, March 15, 1956.

Epidemiology of Lung Cancer

New Zealand led the world in the number of cigarettes smoked per capita of population until 1925. Deaths from bronchial carcinoma in the past five years occurred in men who commenced smoking in the 1914–1918 war. Smoking habits are acquired before age 30 and seldom change after this. Between 1910 and 1925 there was an increase of cigarette consumption in New Zealand of 100 per cent. Between 1940 and 1954 the number of deaths from cancer of the lung and bronchus increased threefold. This increase is explicable by the vast increase of cigarette consumption, and herein lies hope of dealing with the epidemic, the peak of which is not yet in sight.

Joules, H.: The epidemiology of lung cancer in New Zealand. [Letter to the Editor.] Lancet 1: 163, Jan. 21, 1956.

Cancer of the Respiratory Tract in Bantus

As far as is known, an exceptionally high incidence of carcinoma of the nose and accessory sinuses is found only in the South African Bantu. For the most part these tumors are well-differentiated squamous carcinomas with infrequent lymph-node and distant metastases even when far advanced. The extensive practice of snuff taking may account for the high incidence of the tumors of the nose and sinuses. Chemical analysis of snuffs used by Bantus showed the presence of 3,4-benzpyrene, a strong carcinogen, and of 1,12-benzperylene, a weak carcinogen. Heavy cigarette smoking is not common among the Bantus.

Keen, P.; De Moor, N. G.; Shapiro, M. P.; Cohen, L.; Cooper, R. L. and Campbell, J. M.: The aetiology of respiratory tract cancer in the South African Bantu. Keen, P.; De Moor, N. G.; Shapiro, M. P., and Cohen, L.: Part I. Clinical aspects. Cooper, R. L., and Campbell, J. M.: Part II. Chemical identification of carcinogens. Brit. J. Cancer 9: 528-538, Dec., 1955.

Smoking and Lung Cancer

The increase in lung cancer in males in Norway follows closely the pattern of development in other countries but with a delay of a decade or two. Correlation of Norwegian smoking habits with incidence of cancer of the lung confirms results obtained in other countries: that there is a close relationship between tobacco smoking and the development of group-I tumors (epidermoid, squamous-cell, large-

cell, and small-cell carcinomas) in males but not in females, and that there is no relationship between smoking and the development of group-II tumors (adenocarcinomas, bronchiolar-cell carcinomas, benign and malignant adenomas, and salivary-gland tumors of the lungs). Ninety per cent of all lung tumors in Norwegian females are of group II, but less than 20 per cent of lung tumors in males are of this group. Four out of five cases of group-I lung tumors in males in Norway are related to tobacco smoking. Industrial dusts and fumes add an aggravating factor to the injury of tobacco smoking in causing lung cancer. A biological sex difference, morphological or biochemical, cannot be excluded as influencing the response of the lungs to carcinogenic agents. It is highly improbable that the use of tobacco and the development of lung cancer are two quantitatively corresponding manifestations of another underlying primary causative factor. No such factor has been found or even reasonably suggested. Results of this study are so systematic and clear that it is only reasonable to consider the findings as expressions of true conditions. An artifact with such a degree of consistency is most improbable.

Kreyberg, L.: Lung cancer and tobacco smoking in Norway. Brit. J. Cancer 9: 495-510, Dec., 1955.

Mortality Trends in Lung Cancer

From statistical studies of mortality from lung cancer in the United States between 1941 and 1950, it is concluded that, although it is certain that there has been a substantial increase in the incidence of lung cancer in both men and women, the increase is considerably less than the twenty-six-fold for men and sevenfold for women calculated from the simple age-adjusted death rates without consideration of the errors in diagnosis. It is calculated, by assuming a reasonably probable diagnostic error of 2 per cent in persons 35 years of age or older, that the twenty-six-fold and sevenfold increases since 1941 are reduced respectively to fourfold and 30 per cent. It is further shown that the diagnostic error in the earlier years would probably be greater than 2 per cent, further reducing the present, apparent acceleration in the incidence of cancer of the lung.

Gilliam, A. G.: Trends of mortality attributed to carcinoma of the lung: possible effects of faulty certification of deaths to other respiratory diseases. Cancer 8: 1130-1136, Nov.-Dec., 1955.

Epidemiology of Lung Cancer

The following model of relative risks of lung cancer among cigarette smokers derived from the several retrospective and prospective studies was determined to be compatible with more broadly based epidemiological data: nonsmokers, 1; discontinued smokers, 3; smokers—half to one pack, 8; more than one pack, 13. The epidemiological information concerning the distribution of cigarette-smoking patterns in the United States population included the sex, white:nonwhite, urban:rural, and regional ratios of lung-cancer mortality and morbidity. The sex-ratio deviation may represent a basic male-female difference in mortality from neoplastic disease in general and from many non-neoplastic causes as well. The urban-rural deviation represents a real manifestation of multiple environmental factors in lung cancer. The association between smoking and an increased risk of lung cancer must now be accepted. And this risk progresses in an orderly pattern with the amount of smoking.

Haenszel, W., and Shimkin, M. B.: Smoking patterns and epidemiology of lung cancer in the United States: are they compatible? J. Nat. Cancer Inst. 16: 1417-1441, June, 1956.

Smoke Intake

The measure of smoke intake customarily used in statistical studies of cigarette smoking is the number of cigarettes or packages smoked per day. This is inaccurate and may be made more exact by observing the smoker without his knowledge from the time he lights his cigarette until he puts it out, timing on a stopwatch the cumulative time between puffs, measuring the butt, burning a control cigarette for the exact period of cumulative time between puffs, and comparing the lengths

of the two butts—the difference being the length of cigarette burned into the smoker's mouth. One of the crucial points in relating cigarette smoking to bronchogenic carcinoma is the accurate measurement of smoke burned into the smoker's mouth. In seventeen subjects tested as stated a twentyfold variation was found in smoke intake from one cigarette. To classify smokers as light, medium, heavy, etc., from the number of cigarettes consumed per day is, therefore, obviously not justified.

Hilding, A. C.: On cigarette smoking, bronchial carcinoma and ciliary action. I. Smoking habits and measurement of smoke intake. New England J. Med. 254: 775-781, April 26, 1956.

Lung Cancer and Economic Status

A statistical study of 291 cases of cancer of the lung, 235 in men and fifty-six in women, in New Haven, Connecticut, showed an incidence rate per 100,000 of 19.7 in men and 4.5 in women. In men the incidence of lung cancer, unlike that of cancer of other sites, levels off after the age of 55, but not in women. These differences in sex incidence and age gradient between men and women may be important to a better understanding of etiology. The incidence of cancer of the lung was found to be about 40 per cent greater among patients of lower socioeconomic status. Since cigarette smoking is probably not more widespread among the poor than among the other socioeconomic classes, it is concluded that some environmental factor in addition to cigarette smoking contributes to the causation of lung cancer as was reported by Hueper and by Stocks.

Cohart, E. M.: Socioeconomic distribution of cancer of the lung in New Haven. Cancer 8: 1126-1129, Nov.-Dec., 1955.

Supervoltage Roentgen Rays in Lung Cancer

Although little can be expected from supervoltage roentgen-ray therapy in the cure of lung cancer, it is of significant value in palliation. Surgery is the treatment of choice for early cases and the radiotherapist must do what he can with the less favorable remainder. At the Saskatchewan Cancer Clinics from 1932 to 1953, 611 cases of cancer of the lung were diagnosed. The average survival in the 151 cases treated with roentgen-ray therapy alone was but little better than in the untreated, most advanced cases. The average survival of patients treated with the cobalt unit or betatron is considerably better. Combining roentgen-ray therapy with nitrogen-mustard therapy gave longer survival periods than did either alone. Of 319 untreated patients, two were living at the end of three years. Only one patient had a five-year survival after pneumonectomy. More marked palliation was yielded by the betatron than by the cobalt unit. Of twenty-seven patients treated with the 23 Mev betatron, five patients are still alive, the longest survivor for forty months. The cobalt unit was used in fourteen cases: eleven were treated with large fields and the remaining three with smaller fields to the primary tumor only, using rotational therapy. All of these three patients who were treated with rotation are alive and well at the present time, although the longest survival is only nine months. Maximum palliation was obtained from combined therapy with nitrogen mustard and the betatron.

Watson, T. A.: Supervoltage roentgen therapy in cancer of the lung. Am. J. Roentgenol. 75: 525-529, March, 1956.

Radiotherapy of Lung Cancer

Thirty-three patients with carcinoma of the lung were treated with roentgen rays. A dose of 5000 to 5500 r was delivered to the tumor if the carcinoma was squamous cell, and 4000 to 4500 r, if it was undifferentiated. Daily dosage was varied according to the patient's condition. The whole course of treatment usually lasted seven to eight weeks. Four of the twelve patients followed up for five years are alive and well. This 33 per cent survival rate is similar to that from surgical treatment. There is no immediate mortality after radiotherapy, whereas the operative mortality is about 10 per cent. Cerebral metastases seemed to be less common

than after surgical intervention. The results in this small series suggest that radiotherapy in selected cases may be an adequate alternative to surgery.

Smart, J., and Hilton, G.: Radiotherapy of cancer of the lung: results in a selected group of cases. Lancet 1: 880-881, June 9, 1956.

Static Mass Radiography

In a three-year period, the chests of 87,261 adults, approximately one fifth of the population, were examined by means of a static mass miniature radiography unit in the Metropolitan Borough of Islington. As a by-product of this tuberculosis case finding, 115 cases (1.3 per 1000) of lung cancer were discovered. Most of these were in men more than 45 years of age. Nineteen of the patients were women and ninety-six were men. Advantages of the static over the mobile unit are that examinees are obtained from all sources and social classes rather than from only organized groups and mainly from Class III of the Registrar-General's Classification of Occupations, the proportion of first examinations is high with the static and low with the mobile unit, and case yield is persistently high with the static and declines with the mobile unit.

Brett, G. Z.; Benjamin, B.; Craig, J. W., and Freeman, V.: Static mass radiography in a London borough. Brit. M. J. 1: 719-722, March 31, 1956.

Smoking and Coughing

The heavy cigarette smoker who presents with cancer of the lung has had a "smoker's cough" for years and an inflamed, irritated respiratory tract whose lining cells are constantly stimulated to replacement with undamaged cells. Some fine day the replacement process shows signs of wear and tear, and cancer cells are produced. If this theory of irritation is valid, search for carcinogens in tobacco smoke is futile. Lung cancer could result equally from smoking brown paper or cabbage leaves. Pipe smoking causes less coughing and less bronchial carcinoma than does cigarette smoking.

Young, J. A. B.: Smoking. [Letter to the Editor.] Lancet 1: 862, June 2, 1956.

Metastatic Pulmonary Cancer

The presence of pulmonary metastases should not be considered necessarily indicative of a fatal prognosis. In selected cases, the surgical excision of metastatic malignant lesions of the lung has been shown to be technically feasible and productive of a significant group of long-term survivors. Thoracotomy is recommended whenever a patient with a controlled primary cancer has a discrete pulmonary lesion. Excision of a metastatic growth is often possible, and, in some patients, a second primary tumor may be discovered. The patient should be carefully examined to detect extrapulmonary metastases; these are rarely amenable to surgical intervention. Pulmonary resection is not attempted when the recurrent laryngeal or phrenic nerve is involved, pleural effusion has occurred, or the tumor has extended into the chest wall. Prognosis is best if the lesion is confined to one lobe or segment. Localized, accessible, resectable metastases are somewhat more common with sarcoma than with carcinoma. A significant number of pulmonary lesions in patients who have had malignant disease are actually second primary tumors rather than metastatic growths. Such tumors are likely to spread rapidly, in contrast to metastatic growths, which may remain localized for long periods. Since the only reliable means of differentiating metastatic and primary growths is histological study, resection should be done early.

Kelly, C. R., and Langston, H. T.: The treatment of metastatic pulmonary malignancy. J. Thoracic Surg. 31: 298-315, March, 1956.

Etiology of Bronchogenic Carcinoma

E. Cuyler Hammond, Sc.D.

Bronchogenic carcinoma, by definition, is a malignant neoplasm arising in the bronchial epithelium. This is a beautifully simple tissue. On cross section, it appears microscopically as one row of small, round basal cells lying on the basement membrane and one row of ciliated columnar cells interspersed with goblet cells. However, two rows of basal cells are seen so frequently that there is doubt on whether a second row of these cells should be considered as in any way abnormal. Under normal conditions, the surface is bathed in mucus secreted by the goblet cells and the motion of the cilia tends to wash out small particles that fall upon it.

Throughout life, this delicate tissue is exposed to a flow of air reversing directions on the average of about fifteen times per minute. As a rough estimate, the average adult draws about 250,000 cubic feet of air into his lungs each year and a person of age 50 will perhaps have inhaled about 12,000,000 cubic feet of air during the course of his life. Presumably, pure air would not damage the cells, since they must have developed a resistance to any such potential harm by natural selection during the long course of evolution. However, in modern times a new factor has been added. As a by-product of civilization, man has contaminated his air supply with a great variety of particulate, vaporous, and gaseous impurities. Many of these are toxic or highly irritating; some are known carcinogens; and others are suspected of having either carcinogenic or cocarcinogenic properties.

Under the circumstances, it should not be surprising to find cell changes resulting from exposure to such substances. "But," in the words of William E. Smith, "when confronted by noxious influences, what is there for a cell to do but die, or make more or less recovery, or respond with enhanced vigor, even to the extent of unruly growth?" As will be described later, there is strong evidence that, when exposed to inhalants of several different types, cells do indeed "respond with enhanced vigor" in the form of growth (or more strictly, the growth of cell populations) of benign and malignant types in bronchial epithelium.

The first indication[21] of this came in the sixteenth century when a high mortality rate from a strange lung disease was found among miners of the Erzgebirge in Saxony. In 1879 Haerting and Hesse[16] identified the disease as cancer of the lung and noted its occurrence in 75 per cent of deceased workers in these mines. This was twenty-one years before the discovery of natural radioactivity and thirty-nine years before cancer was produced experimentally with carcinogenic material.[58] Nevertheless it would have been hard to escape the conclusion that the extraordinary incidence of an otherwise rare disease was somehow related to the occupation of these men. The only alternative hypothesis that I have heard proposed is that the workers in these mines may have been of a highly inbred stock and the disease a result of their heredity.[41]

The principal ores of the Schneeberg mines are sulfides and arsenides of nickel and cobalt and the Joachimsthal mines contain these substances plus silver and a high content of pitchblende and radium. Before the cancer-producing potential of ionizing radiations was known, it was thought that arsenic and cobalt were the principal etiological factors; and it is quite possible that they were contributory. However, the work of Loewy[32] in 1929, Sikl[43] in 1930, and the experimental production of lung cancer in rats exposed to aerosols of radioactive cerium and plutonium by Lisco[31] in 1947 have convinced most investigators that the radioactivity of the dust is primarily responsible for the occurrence of lung cancer at Joachimsthal. The occurrence of lung cancer among the

processors of radium ores, reported by Baader, Teleky, and Nietzel[3] supports this position and serves to rule out the heredity hypothesis already mentioned.

Regardless of which particular element (arsenic, nickel, cobalt, uranium, or radium) is the principal etiological factor, one fact seems to have been established beyond any reasonable doubt: occupational exposure to dust (and perhaps radon gas) caused lung cancer among Joachimsthal miners. Knowledge of this fact alone is sufficient to indicate preventive measures in such mines.

Three substances besides radioactive materials have been quite conclusively demonstrated to be causes of lung cancer among heavily exposed workers. These are chromates, nickel, and hot gases from tar and dusts at the illuminating-gas generators in a Japanese steel mill. In each instance, the conclusion rests primarily upon evidence of a high lung-cancer rate among workers so exposed. Arsenic, which can produce skin cancer in man, has long been suspected as a cause of lung cancer, but there are differences of opinion on whether or not this is so.[23, 47] Hueper,[25] who has studied the problem intensively, has expressed the opinion that workers in various industries are exposed to a great many different substances (in the form of dusts, gas, or vapor) that are of etiological significance in lung cancer. He may prove to be correct, but most investigators seem to feel that there is as yet insufficient evidence on which to base definite conclusions concerning occupational exposures other than those just named. Nevertheless, there are suggestive data concerning a number of occupational groups such as hot-metal workers, asbestos workers, painters, and workers exposed to excessive fumes of gasoline, oil, or varnish.[5, 53] It is also quite possible that newly discovered industrial products and processes carry dangers for the future. Unfortunately, there is no way fully to assess these possible hazards until human beings have been exposed for many years.

It may seem strange that doubt and differences of opinion remain on so many of these questions after years of research by very competent investigators. I can suggest two reasons. The first is statistical. Evidence at hand suggests that lung cancer occurs only after many years of exposure to a carcinogenic situation. Now, unless an agent is extremely potent (i.e., sufficient to cause a five- or ten-to-one increase in lung-cancer–incidence rates) thousands of people, all exposed for many years, have to be studied in order to prove that the lung-cancer–incidence rate among them is actually greater than the average for the general population. Considering the turnover of labor, the small number of employees in most individual plants, the lack of adequate records from prior years, and the difficulty of estimating the degree to which workers were exposed to some specific substance five to twenty years ago, it is difficult to find sufficiently large and suitable groups on which to make reliable studies. Thus a factor of real danger for perhaps several thousand workers could easily go unnoticed or unproved. The second reason is this: Some of the substances suspected as possible causes of lung cancer are known to produce serious, non-neoplastic lung disease (e.g., asbestosis). In the United States and some other countries, industrial hygienists have done excellent work in protecting workers from high exposure to such substances. In so doing they may have prevented lung cancer as well. At the same time, by reducing the lung-cancer hazard (if any), they may have made it impossible to determine whether a real hazard ever existed. While this may be disappointing to some scientists, from the standpoint of the workers it can hardly be deplored.

It would be of tremendous help if animal experimentation alone provided sufficient evidence for determining whether a suspected substance actually causes lung cancer in man under ordinary conditions of exposure. Unfortunately, this is not the case. The difficulty is that different species of animals, as well as different strains of the same species, vary enormously in their reactions to potential carcinogenic substances. When a particular carcinogen is applied to different tissues of the same strain of animal, carcinoma may develop

in one tissue, hyperplasia or metaplasia may develop in another tissue, and no change at all may occur in a third tissue. The method of application, the concentration and duration of exposure, the physical state of the substance, the presence or absence of some other substance or condition (e.g., a solvent or a cocarcinogen), all influence the probability that a particular erstwhile carcinogen will actually produce cancer. Furthermore, under certain conditions, a noncarcinogenic substance or action may be a factor in the causation of cancer by creating conditions under which a carcinogenic agent in the environment can produce cancer. For example, shaving does not produce cancer, but shaving the hair from the back of a mouse before applying a weak carcinogenic agent permits the agent to come into direct contact with the skin and thereby enhances the effect.

For these reasons, one must be extremely cautious in drawing conclusions as to cancer in man from the results of experiments performed on other species. Nevertheless, animal experimentation is useful in studying the mechanisms of carcinogenesis. In addition, if a substance causes cancer in mice, rats, or rabbits, this suggests that it may cause cancer in man; but the reverse is not true (i.e., the negative result of an animal experiment is no indication that a certain substance is safe for man).

Campbell[6, 7] carried out a long series of inhalation experiments in which he exposed mice to dusts and gases of at least nineteen different types, including pitchblende, iron oxide, tarred road dust, nickel, silicon dioxide, steel grindings, exhaust gases from gasoline engines, cigarette smoke, anthracite coal, and coal soot. With only two exceptions, more lung tumors developed in the exposed mice than in the control mice. The consistency of the effect from such a large variety of substances was impressive even though with some substances the difference between the exposed and control groups was small and might have been due to chance. It is interesting that the exceptions were anthracite coal and coal soot, particularly since the latter can cause cancer of the scrotum in man. In similar experiments, Essenberg[12] found an increased incidence of lung tumors in mice exposed to cigarette smoke, but Lorenz and his associates[34] found no effect on mice exposed to tobacco smoke from a pipe. McDonald and Woodhouse[36] observed an increased frequency of adenomas in the lungs of mice exposed to dust collected from the air of an English city.

A question has been raised of whether the mouse is a suitable animal for such experiments, since spontaneous lung cancer occurring in mice is of a different type from that most frequently found in man. Most of the tumors found in these experiments were adenomas or adenocarcinomas. Vorwald[49] produced a high incidence of definitely malignant tumors in the lungs of rats by exposing them to beryllium oxide. These tumors more nearly resembled the epidermoid type, which is the most common in man.

A great many substances of possible etiological significance in lung cancer have been tested on the skin of mice and other animals. For example, Wynder, Graham, and Croninger[56] painted cigarette-smoke condensate on the skin of mice after shaving off the hair, and carcinoma, as well as papillomas, developed in a high percentage of the animals. The same investigators have more recently produced cancer on the skin of rabbits in the same way. Gellhorn[13] and his associates painted mice with a "subthreshold" dose of benzpyrene and then with tobacco-smoke condensate. More papillomas and carcinomas developed with this combination than with the same dosage of benzpyrene without the tobacco-smoke condensate. He concluded that cigarette-tobacco tar has cocarcinogenic activity under the conditions of the experiment. Wynder and Wright[57] have fractionated cigarette-smoke condensate chemically and tested each fraction on the skin of mice. They found that one fraction, consisting of less than 2 per cent of the original tar, seemed to contain most of the material that is carcinogenic under the conditions of the test. This may or may not indicate that the same fraction contains most of the ma-

terial responsible for the high incidence of bronchogenic carcinoma in cigarette smokers. Kennaway and Waller[29] have analyzed air samples from several English cities and estimate that in seventy years a man living in London would inhale about 12.5 mg. of 3,4-benzpyrene, a substance that is highly carcinogenic when applied to the skin of mice.

The foregoing is only a partial review of a very extensive literature on animal tests of the carcinogenicity of agents possibly related to the lung-cancer problem. One thing is certain: the air breathed by many people—at least by those in certain occupations and places of residence or with the cigarette-smoking habit—contains one or more substances that have been shown to produce neoplastic changes under certain experimental conditions. The question is: which of these various suspects actually contribute to the occurrence of bronchogenic cancer in man? In my opinion, this can only be answered by observations made on human beings.

Only a very small proportion of the 27,000 Americans (23,000 males and 4000 females) who died of lung cancer last year were occupationally exposed to dust containing radioactive substances, chromates, or nickel or to hot fumes from illuminating-gas generators. Perhaps a sizable number had some degree of occupational exposure to other substances of etiological significance. However, a large proportion were engaged in occupations that are almost certainly free of any such hazard (i.e., clerks, salesmen, accountants, lawyers, butchers, teachers, etc.). Therefore, in recent years, research in the field has been concentrated on studies of non-occupational factors to which large segments of the population are exposed.

The rapid rise in lung-cancer–death rates gives strong support to the theory that the great majority of cases (if not all cases) result from extrinsic factors and are not due solely to some hereditary factor. The lung-cancer–death rates in the United States as reported by the National Office of Vital Statistics and standardized to the age distribution of the 1940 population have increased as follows: for males: 0.7 per 100,000 population in 1914, 3.6 in 1930, 9.4 in 1940, and 24.0 in 1953; for females: 0.6 in 1914, 2.1 in 1930, 3.2 in 1940, and 4.3 in 1953. Some of this reported increase was probably due to better diagnosis. However, there is no reason to suppose that doctors are more capable of diagnosing lung cancer in men than in women. The fact that the reported rate increased much more rapidly in men than in women rules out the hypothesis that the rise can be attributed to better diagnosis alone.

The possibility that the rise in lung-cancer–death rates was influenced by the concurrent decline in death rates from pneumonia and tuberculosis has been considered by this writer[17] and others. In 1920, Winternitz, Watson, and McNamara[32] predicted that lung cancer would increase as a result of postinfluenzal pneumonia occurring at the time of the great influenza epidemic. However, Liebow[30] has pointed out that there is little evidence that any large proportion of pulmonary tumors has its basis in the type of lesion associated with postinfluenzal pneumonia. He has also called attention to the fact that lung cancer has not increased disproportionately in Iceland, which suffered heavily from influenza in the great pandemic that followed World War I.

Some hints may be obtained from a study of trends in inhalants of several sorts to which large segments of the general public are exposed. The five most commonly considered are: (1) soot and fumes from coal furnaces, (2) soot and fumes from oil furnaces, (3) fumes from internal-combustion engines, (4) dust from bituminous-surfaced roads and rubber tires, and (5) cigarette smoke.

Since coal soot contains known carcinogenic agents, this was once a prime suspect. However, coal consumption has not been increasing in this country. Therefore, it seems unlikely that coal soot could account for the rise in lung-cancer–death rates in the United States (although it might have some relationship to the problem). As noted previously, anthracite-coal dust and coal soot were the only two in-

(Continued on page 163.)

Current Lung-Cancer Research in the United States*

GENERAL PATHOGENETIC STUDIES

Butt, E. M. Los Angeles County Hosp.	Trace metals in lung and other tissues
Cerecedo, Leopole R. Fordham University	Ribonucleic and deoxyribonucleic acids in spontaneous tumors of mice and rats
Hirsch, James Rockefeller Institute	Sputum cytology in pulmonary carcinoma and respiratory infection
Hoch-Ligeti, Cornelia University of Virginia	Changes produced by carcinogenic irritants in human-lung transplants in rats and in tissue cultures
Kotin, Paul University of Southern California	Fate of labelled carcinogenic polycyclic hydrocarbons deposited in lungs of animals and humans
Leuchtenberger, Cecile Western Reserve Univ.	Cytochemistry, cytology, and histology of organs of animals exposed to tobacco smoke
Mellors, Robert C. Memorial Center for Cancer and Allied Diseases	Cellular localization of tobacco smoke extracts by fluorescence microscopy in mouse skin and buccal epithelium of humans
Nelson, Norton New York University	Influence of particle size on site and degree of retention of mist particles
	Experimental squamous carcinoma of lung
Papanicolaou, George N. Cornell Univ. Medical College	Relation of lung cancer to degenerative changes of ciliated bronchial cells
Rigdon, R. H. University of Texas	Susceptibility of various duck tissues to methylcholanthrene
Rogers, E. Stanfield Duke University	Fertile soil conditions for pulmonary adenomas
Sommers, Sheldon C. Massachusetts Memorial Hosp.	Host factors in lung cancer with special attention to sex differences
Tipton, Isabel H. Oak Ridge National Laboratory	Trace metals in human lungs obtained at autopsy

EFFECT OF TOBACCO ON PULMONARY FUNCTION

Gollan, Frank Vanderbilt University	Search for isotope that will distribute itself along pulmonary lymphatic drainage pathways
Langston, Hiram Hines Veterans Hosp.	Thoracic-duct output of lymphocytes
McKee, Kelly T. Medical College of South Carolina	Vital capacity, maximal breathing capacity, air flow, etc., in smokers and nonsmokers
Moore, George Roswell Park Memorial Inst.	Physiological effects of direct inhalation of tobacco smoke by laboratory animals
Motley, Hurley University of Southern California	Changes of pulmonary function induced by tobacco smoke
Segal, Morris Tufts College Medical School	Effect of tobacco smoking on pulmonary mechanics in smokers and nonsmokers
Zeidman, Irving University of Pennsylvania	Spread of cancer in lymphatic system; effect of thoracic-duct ligation on metastases

*Information supplied in part by Bio-Sciences Information Exchange, Smithsonian Institution, Washington, D. C., by courtesy of Dr. L. Deignan, Director.

HISTOLOGICAL EFFECTS OF TOBACCO ON RESPIRATORY MUCOSA

Auerbach, Oscar East Orange Veterans Hosp.	Relation of smoking to lung cancer; detailed histological study of bronchial epithelium
Cowdry, Edmund V. Washington Univ. School of Medicine	Postmortem study of bronchial epithelium of heavy smokers and nonsmokers
Hawthorne, Herbert Reed University of Pennsylvania	Histological effects of tobacco on respiratory mucosa of dogs
Hilding, Anderson C. Duluth St. Luke's Hosp.	Fate of smoke in lungs; amount of smoke consumed by smokers
Knudtson, Kenneth P. Seattle Veterans Hosp.	Pathological and topographical features of bronchial mucosa of smokers and nonsmokers
Kreshover, Seymour J. Medical College of Virginia	Leukoplakia and susceptibility to tobacco smoke in hamsters
Reimann, Stanley P. Institute for Cancer Research and Lankenau Hosp.	Co-operative study of human lung ailments from autopsy material from various parts of the country
Rhoads, C. P., and Day, E. Sloan-Kettering Institute	Effects of tobacco smoke on respiratory epithelium of smokers and nonsmokers
Schour, Isaac University of Illinois School of Dentistry	Histological changes in respiratory tissues of animals subjected to tobacco smoke
Shubik, Philippe Chicago Medical School	Penetration, localization, and biological action of carcinogenic hydrocarbons in mammalian lung

TOBACCO AS INHIBITING OR POTENTIATING AGENT

Freelander, B. L. San Francisco Mount Zion Hosp.	Tobacco extracts as precarcinogens, cocarcinogens, promoting or initiating agents
Graham, Evarts A. Washington University	Experimental production of skin cancer by tobacco products
Griffin, A. Clark M. D. Anderson Hospital	Effects of tobacco smoke on carcinogenesis of methylcholanthrene, benzpyrene, etc.
Homburger, Freddy Tufts University	Inhibiting effects of cigarette tars on cell growth of transplantable tumors in rodents
Mann, David E. Temple University	Effect of tobacco smoke on methylcholanthrene skin cancers in mice
Nelson, Norton New York University	Carcinogenic substances in tobacco tars
Rhoads, C. P., and Wynder, E. L. Sloan-Kettering Institute	Identification of active carcinogens in tobacco tars

AIR POLLUTANTS

Amdur, Mary O. Harvard School of Public Health	Physiological response of animals and humans to atmospheric pollution
Baetjer, Anna M. Johns Hopkins Univ.	Lung cancer in guinea pigs, rabbits, and rats from hexavalent chromate dusts
	Effects of environmental temperature and humidity on the susceptibility of mice and rats to toxic agents
Bambo, O. N., Jr. Salt Lake City Veterans Hosp.	Metaplastic, atypical, and precancerous lesions from uranium dust in rats
Byers, Horace University of Chicago	Detection and analysis of micron-sized particles retained in the lungs
Hardy, Harriet Massachusetts General Hosp.	Granulomatous reaction and lung cancer from beryllium
Heyroth, Francis University of Cincinnati	Pathological examination of tissues after exposure to beryllium
Kamner, A. G. University of Pittsburgh	Lung hazards from radioactive material

AIR POLLUTANTS (Continued)

Kehoe, Robert A. University of Cincinnati	Pathogenesis of granulomatous and malignant transformations from beryllium
Kotin, Paul University of Southern California	Effect of air pollution in emphysema, asthma, etc. Morphological changes in respiratory tract after exposure to air pollutants using isotopes
Lynch, Kenneth M. Medical College of South Carolina	Asbestosis and carcinoma of the lung
Motley, Hurley L. University of Southern California	Pulmonary function associated with pneumoconiosis in the diatomite industry Effects of inhalation of synthetic or naturally occurring atmospheric pollution
Nelson, Norton New York University	Techniques for biological evaluation of air-borne carcinogens
Phair, John University of Cincinnati	Determination of individuals most likely to show effects of air pollution
Quilligan, James College of Medical Evangelists	Effects of air pollutants on chick embryos, tissue cultures, and mice; influence of virus infection
Schepers, G. W. H. Saranac Laboratory	Cocarcinogenic potentiality of asbestos with beryllium
Vorwald, Arthur J. Wayne University College of Medicine	Pathogenesis of granulomatous and malignant transformations from beryllium

DIAGNOSIS AND THERAPY

Allan, Warde B. Johns Hopkins University	New cytological methods in screening for lung cancer
Ariel, Irving M. Pack Medical Foundation	Effects of radioactive phosphorus on primary and metastatic neoplasms of the lung
Barach, Alvan L. Columbia University	Production and elimination of bronchial secretions in cytological studies
Berg, Harold F. University of Louisville	Distribution of radioactive gold to pulmonary lymph nodes
Boucot, K., and Cooper, D. A. Philadelphia Health & Tuberculosis Association	Radiological survey to delineate characteristics of curable lung cancer
Cohen, Aaron A. San Fernando Veterans Hosp.	Pulmonary function before and after treatment of lung cancer with nitrogen mustard
Gollan, Frank Vanderbilt University	Isolation of particulate radioactive iodinated human serum albumin by pulmonary lymph nodes
Hall, Charles A. Albany Veterans Hospital	Alteration in immunilogical responses to nitrogen mustard in lung cancer
Kaplan, E. Hines Veterans Hospital	Radioactive gold and chromic phosphate in treatment of carcinoma of the lung
Kaplan, William D. City of Hope Medical Research Institute	Value of irradiating pulmonary adenocarcinomas in atmosphere of pure oxygen
Lenz, Morris Columbia University	Clinical evaluation of supervoltage in bronchogenic carcinoma
Lodwick, Gwilyms State University of Iowa	Lung-tumor size, density, and location correlated with histological type
Merrill, Malcolm H. California State Department of Health	Survey of effect of smoke, smoking, and occupation in lung cancer
Sherwood, Charles E. University of Rochester	Natural radiological history of carcinoma of the lung

(Continued from page 159)

halants tested by Campbell that showed no indication of increasing the occurrence of pulmonary tumors in mice.

Fuel-oil sales in the United States have risen rapidly, the annual sales now being about three and a half times as great as in the base period, 1924 to 1926. Soot and fumes from this source are now probably a major source of air pollution in American cities.

The increase in fumes from motor vehicles is shown in two ways. The number of motor vehicles now registered in the United States is nearly three times as great as in the base period, and motor-fuel consumption is more than five times as great. Although no exact measure is available, traffic congestion in cities and highways near cities has probably risen to an even greater degree. Therefore the increase in fumes from this source, particularly in cities, is really tremendous.

A certain amount of fine dust in the air comes from road surfaces. High-type bituminous roads under state control have increased nearly sixfold since 1924 to 1926. Other types of roads surfaced with asphalt and oil products have increased to such a degree that they could not even be shown on the chart without increasing the scale.

Cigarette consumption in the United States has increased from about 3 billion per year in 1900, to 98 billion per year in 1925 to 1929, to 398 billion per year in 1953. This is partially due to the increase in the population. Furthermore, the extent of the increase during the last few years is obscured by the trend toward the use of king-size cigarettes. Therefore, a better index for our purposes is given by the pounds of cigarette tobacco consumed per year per adult (i.e., per person more than 15 years old). There has been almost a fourfold increase in the index of cigarette consumption since 1924 to 1926.

In addition to being exposed to the inhalants just named, some groups in the general population are exposed to high concentrations of a wide variety of other air pollutants. For example, people living in the near vicinity of certain industrial plants may be exposed almost as heavily as the employees to dusts, chemical smokes, and exhaust fumes. Conversely, workers with occupational exposure to factors of possible etiological importance in lung cancer also may be heavy cigarette smokers, as well as being exposed to the same general air pollutants as their neighbors.

An indication that general air pollution, as well as occupational exposures of various types, may contribute to the incidence of lung cancer comes from the fact that lung-cancer–death rates are reported to be higher in urban areas than in rural areas. This difference is greater in males than in females. However, a nationwide survey conducted by the Bureau of the Census in co-operation with the National Cancer Institute[13] shows that heavy cigarette smoking is much more common in city dwellers than in the rural population and is more common among men than among women, particularly in the older age group. These differences in smoking habits partially account for the urban-rural differences in lung-cancer–death rates and probably account for some of the difference in lung-cancer–death rates between men and women.[14]

Some scientists have reasoned as follows: When a carcinogenic agent is applied to tissue, several changes, such as hyperplasia and metaplasia, usually precede the appearance of cancer. If the agent is applied over a wide area, independent foci of carcinoma are apt to appear in several different places although one primary lesion may develop and spread much more rapidly than any of the others. Therefore, if inhalants of any sort (i.e., industrial fumes or dust, general air pollutants, or cigarette smoke) cause most cases of bronchogenic carcinoma, then one would expect to find hyperplasia, metaplasia, and perhaps carcinoma in situ widely scattered in the remaining bronchial epithelium of people who have died of the disease. Furthermore, one would expect to find similar changes, but to a less marked degree, in the bronchial epithelium of persons who died of some other cause but who had

been heavily exposed to any one of the implicated inhalants.

This hypothesis has recently been tested by Auerbach[1, 2] and his associates. Their procedure was to dissect out the tracheobronchial tree and divide it into 180 to 200 blocks, each of which was embedded in paraffin. One slide was prepared from each block and was studied microscopically. The findings on thirty-four white males who died of bronchogenic carcinoma (and all of whom had been smokers) were as follows: Marked basal-cell hyperplasia (five or more cell rows in thickness) was found in every case. The average was 15 per cent of the slides per case with this finding. Stratification of the epithelium was found in all but two cases and squamous metaplasia was found in all but three (the average being 13.4 per cent and 11.7 per cent of the slides respectively). Carcinoma in situ (as defined by Black and Ackerman[4]) was found in twenty-six of the thirty-four cases, the average percentage of slides with the finding being 6.3 per cent. An additional 6.7 per cent of the slides had borderline lesions that might or might not have been true carcinoma in situ. In the typical case, lesions of these four types (basal-cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ) were found widely scattered throughout the remaining bronchial epithelium of men who died of bronchogenic carcinoma. This is consistent with the hypothesis that the disease was caused by some substance or substances inhaled into the lungs.

The same investigators studied the bronchial epithelium of eighty-three white males who died of causes other than bronchogenic carcinoma. All of them had lived in urban areas and presumably had been exposed to general air pollutants. Sixteen had never smoked regularly, twenty had smoked cigarettes regularly but less than a pack a day, and forty-seven had regularly smoked one pack or more of cigarettes a day.

Among the one-pack-or-more a day cigarette smokers the occurrence of basal-cell hyperplasia, stratification, squamous metaplasia, and definite carcinoma in situ was only slightly less than among men who died of lung cancer as just described. The occurrence of lesions of these four types was considerably less among the less-than-one-pack a day cigarette smokers and far less among those who had never smoked regularly. Thus the findings were consistent with the theory that cigarette smoking is a very important etiological factor in bronchogenic carcinoma.

It is of interest that some changes of the types described were found in the bronchial epithelium of the men who had never smoked regularly. Since all of these men had lived in urban areas, some of the lesions may have been due to exposure to general air pollutants. None of these sixteen men had been engaged in occupations that are highly suspect although several were bus drivers or garage workers.

Chang[6] has recently reported the results of a somewhat similar study of bronchial epithelium. He found: (1) distended goblet cells to be more numerous in smokers than in nonsmokers, (2) the average length of the cilia to be less in smokers than in nonsmokers, (3) the average thickness of the epithelium to be greater in smokers than in nonsmokers, and (4) bronchial metaplasia to be present in a greater percentage of the smokers than the nonsmokers.

Physiological effects of various sorts can be produced by extraordinarily small quantities of potent compounds. Nevertheless, some people have wondered how the small quantity of material contained in tobacco smoke could be sufficient to produce such an effect as cancer even when the exposure is continued over the course of a lifetime. Furthermore, ciliary action ordinarily washes out material deposited on the surface of the bronchial epithelium.

Recent experiments conducted by Hilding[22] on the lungs of freshly killed calves has thrown new light on the subject. The cilia remained active for some time after the death of the animal. Hilding drew cigarette smoke through the trachea and bronchial tubes and quickly thereafter destroyed the cilia in a small area. The action of the cilia in the surrounding area

resulted in a concentration of tobacco tar in some of the deciliated areas.

From this, it is reasonable to suppose that tobacco-smoke tar and other inhaled materials accumulate in deciliated areas of squamous metaplasia, such as were found in human lungs by Auerbach and his associates and by Chang. In addition, it will be recalled that Chang found the average length of the cilia to be less in smokers than in nonsmokers. Kotin[27] studying rats and rabbits has reported that exposure to air pollutants and to tobacco smoke interfered with particle movement, permitting accumulation on the bronchial epithelium.

While it is unknown what components of cigarette smoke and certain air pollutants interfere with ciliary action, there is no particular reason to assume that the same components have a direct carcinogenic effect. The mechanism may perhaps be similar to the effect of shaving the hair from the skin of a mouse before painting on a carcinogenic agent. One component may destroy the natural protective mechanism (i.e., ciliary action) leaving the tissue exposed to the action of another component that is carcinogenic.

From the foregoing it should be clear that there is no lack of pathological evidence, no lack of experimental evidence, and no lack of general evidence (i.e., time trends, urban-rural differences, sex differences, etc.) in support of the theory that inhalants to which large segments of the population are exposed play an etiological role in bronchogenic carcinoma. Of course, the exact mechanisms are not yet fully known and much research remains to be done; but the gaps are being filled in rapidly.

Now let us consider the evidence bearing on this question: Are cigarette smoking and exposure to general air pollutants factors of real practical importance in the etiology of bronchogenic carcinoma? In other words, are lung-cancer–death rates very much higher among people subjected to one or both of these two hazards than among people not subjected to them?

Fortunately, there is a wealth of information available to answer this question, particularly in respect to cigarette smoking. In medical history there have been very few subjects so thoroughly studied by so many competent, independent investigators. Most remarkable is the fact that every group of investigators that has actually collected data systematically on the subject has arrived at the same conclusion: namely, there is a very high association between smoking habits and the occurrence of lung cancer. In the opinion of this writer[18, 19] no reasonable doubt any longer exists on that point. Not so many studies have been made on general air pollution in relation to lung-cancer–death rates, but such as have been made indicate that this factor is also of importance.

In reviewing scientific literature, one usually finds that purportedly new findings were reported by some investigator decades if not centuries earlier. So far as I can ascertain, Hoffman[24] was the first person to present evidence that lung cancer (and cancer of several other sites) might be related to smoking habits. Acting on this lead, Lombard and Doering[33] made a beautifully controlled study of the smoking habits of cancer patients as compared with the smoking habits of a matched series of well persons. They found a higher proportion of smokers among the cancer-patient group than in the control group. Their findings, published in 1928, seem to have made little impression upon the scientific community. In 1938, Raymond Pearl[39] presented evidence that death rates (all cancer combined) were higher among smokers than among nonsmokers. This only caused a slight flurry of comment (based largely upon a charge by "old curmudgeon," Harold Ickes) that newspapers were suppressing evidence because of pressure from their advertisers —a charge that Pearl denied. Between 1939 and 1955, fifteen independent groups of investigators[5, 9, 28, 29, 35, 37, 38, 40, 42, 44, 45, 50, 51, 53, 54] in Germany, the United States, the Netherlands, England, and Finland published reports on the subject, all of which showed a much higher proportion of smokers among lung-cancer patients than among control groups.

For certain statistical reasons, some in-

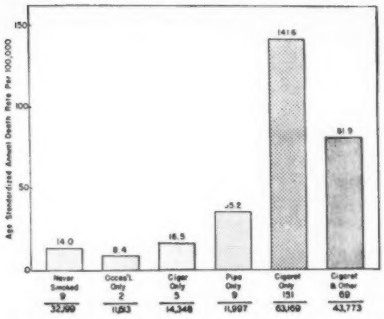

FIGURE 1. Carcinoma of the lung. Lifetime cigarette smoking.

vestigators, the present writer included, were unwilling to accept the evidence collected up to 1951 as conclusive proof that smoking causes an increase in lung-cancer–death rates. For this reason, three studies of a different type were inaugurated.[10, 11, 20] These were all based upon the principle of questioning a large number of people about their smoking habits and then tracing them for several years. The first results of two of these studies were published in 1954. The results of the third have not yet been reported.

Doll and Hill[10] questioned British physicians about their smoking habits. The first preliminary report of their findings, published in June of 1954, was confined to 24,389 male doctors, 789 of whom died within the first twenty-nine months of the study. No lung-cancer deaths occurred among 3093 of the doctors who were nonsmokers; but twelve lung-cancer deaths occurred among 8431 doctors who smoked 1 to 14 gm. of tobacco a day, eleven lung-cancer deaths occurred among 7662 doctors who smoked 15 to 24 gm. of tobacco a day, and thirteen lung-cancer deaths occurred among 5203 doctors who smoked 25 or more gm. of tobacco a day. No distinction was made among cigarette, pipe, and cigar smoking. However, the authors give data that point to cigarette smoking as having a higher association with lung cancer than pipe smoking. The death rate from coronary thrombosis was also found to increase with the amount of smoking.

Hammond and Horn,[20] with the assistance of some 22,000 volunteer workers of the American Cancer Society, collected smoking histories on a very large number of white men who were between the ages of 50 and 69 years in the first half of 1952. This was carried out in 394 counties in nine states, the areas covered varying in type from rural to large industrial cities. A total of 186,352 men who were reported to be alive as of November 1, 1952, were traced for the ensuing two years (i.e., through October 31, 1954). During that period of time 246 died of lung cancer. The most recent findings available from the study may be summarized briefly as follows:

The men were first divided into groups according to their lifetime history of smoking (Fig. 1). The lung-cancer–death rate of those who had never smoked was very low, being only 14.0 per 100,000 per year. The lung-cancer–death rate was ten times as high (141.6 per 100,000 per year) among men with a history of having smoked cigarettes regularly but not cigars or pipes. The rates for occasional smokers and for cigar smokers were about the same as for those who had never smoked, but pipe smokers had a higher rate (35.2). Men with mixed smoking habits (cigarettes and also cigars or pipes) had a lung-cancer–death rate lower than that for the cigarette-only group but much higher than any of the other groups.

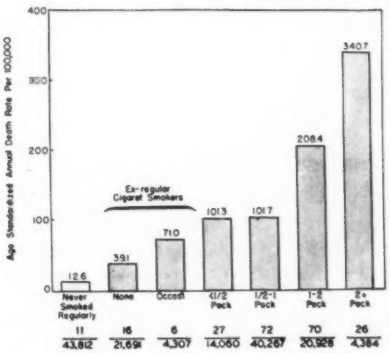

FIGURE 2. Carcinoma of the lung. Current cigarette smoking at time of questioning.

Next, the men with a history of having smoked cigarettes regularly at some time during their lives were classified according to their cigarette-smoking habits extant at the time of questioning (Fig. 2). The lung-cancer–death rate of men who smoked two or more packs of cigarettes a day was more than three times as high as the rate for men who smoked cigarettes regularly but less than a pack a day. The rates for ex-regular cigarette smokers were less than for those who were smoking cigarettes regularly at the present time.

Finally, the men were classified as to their place of residence as well as to their smoking habits (Fig. 3). Both for smokers and for those who had never smoked regularly, the lung-cancer–death rates were higher in the urban than in the rural areas. When the data were standardized for smoking habits as well as for age, the lung-cancer–death rate was 78.7 per 100,000 per year in cities of 50,000 or more population as compared with 60.0 in rural areas, a difference of 31 per cent.

Heavy cigarette smokers had higher death rates than nonsmokers from coronary-artery disease and from cancer of sites other than the lungs.

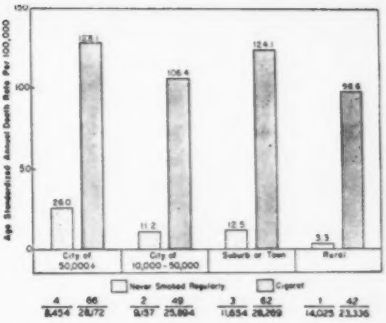

FIGURE 3. Carcinoma of the lung. Classification according to residence.

Stocks and Campbell[48] are conducting a study of air pollution and smoking habits in relation to lung-cancer–death rates in three areas: (1) a densely urban area with much air pollution (Liverpool), (2) a mixed urban-rural area with some air pollution (an area in the western part of England including the cities of Chester and Wrexham), and (3) a rural and small town area with very little air pollution (Anglesey and Caernarvon counties in northern Wales). Their preliminary find-

TABLE 1

Lung-Cancer-Death Rates per 100,000 Male Population per Year by Smoking Habits and by Place of Residence

Data from Studies by Hammond and Horn (U.S.A.) and by Stocks and Campbell (Great Britain)

Study	Hammond & Horn	Stocks & Campbell		
Time period	Nov. 1, 1952-Oct. 31, 1954	Mid-1952—mid-1954		
Age group	50-75 yr.	45-74 yr.		
Location	394 counties U.S.A.	Caernarvon & Anglesey counties, Wales	Chester-Wrexham area, Eng.	Liverpool, Eng.
Type of area	Mixed	Rural*	Mixed	Urban
Nonsmokers	14	14	0	131
Pipe smokers	35	41	25	143
Cigarette smokers†				
Light	101	87	153	297
Moderate	208	183	132	287
Heavy	341	363	303	394

*A part of the population of Caernarvon and Anglesey counties lives in towns that would be classified as nonrural by the definition used in the American study.

†The method of classification by amount of cigarette smoking is somewhat different in the two studies.

ings are summarized in Table 1, which also shows our findings for comparison.

Considering sampling variations and the somewhat different methods of classification used in the two studies, the lung-cancer–death rates by smoking habits as found in the American study are remarkably close to the findings of Stocks and Campbell in the two areas they describe as "rural" and "mixed." The big difference is in the lung-cancer–death rates in Liverpool as compared with the two other areas in the British study. Of this the authors say: "this suggests that the Liverpool environment exposes men to a carcinogen which adds about 100 to the death rate per 100,000 from lung cancer, whether they smoke or not . . . ."

From our findings, it might have been said that "they suggest that the environment of a number of American cities of over 50,000 population exposes men to a carcinogen which adds about 20 to the death rate per 100,000 from lung cancer, whether they smoke or not." The findings of both studies suggest that heavy cigarette smoking adds more than 300 to the death rate per 100,000 whether or not men are exposed to factors related to urbanization. It should be noted that the foregoing comparisons apply to men of the specified age range.

Why should the lung-cancer–death rates be so much higher in Liverpool than in a population drawn from a number of American cities?

It seems to me that the most probable answer is about as follows: Cities vary greatly in degree of air pollution, in the chemical composition of the pollutants, and in exposure related to occupation. From the evidence it appears that the bulk of the urban population in the American study was drawn from cities (or parts of cities) more like Chester and Wrexham than like Liverpool in these respects. It is not unlikely that lung-cancer hazards in some American cities are as severe as in Liverpool. This should be thoroughly investigated.

Another possible explanation might be this: For many years there has been a steady shift in the population of the United States from rural to urban areas. In terms of exposure to air pollutants, this has been slightly compensated for in recent years by movement from the central areas of large cities to suburban areas. It may be that the central areas of some of our industrial cities are like Liverpool; but most of the present population now residing in such areas may not have been there long enough for a resultant large increase in the lung-cancer–death rate to occur as yet. If this be the case, then it is of the utmost importance that remedial action be taken as soon as possible.

Stocks and Campbell are making chemical analyses of samples of particulate impurities collected from the air in each of their three study areas. They have been especially interested in the carcinogen 3,4-benzpyrene, which is present in measurable quantities in the air of Liverpool and which has also been found in very small amounts in cigarette smoke. However, air contamination (as well as cigarette smoke) is made up of a multitude of different substances and 3,4-benzpyrene is only one of many under investigation. In my opinion, gases should not be overlooked in these studies, particularly carbon monoxide, which is present both in city air and in cigarette smoke.

References to articles mentioned are available upon request. Address:

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Current Status of Lung-Cancer Research

Some Pathogenetic Aspects

Dean F. Davies, M.D., Ph.D.

Reported Research

More than a year and a half ago the Minister of Health of Great Britain summarized in the House of Commons the considered judgment of the Standing Advisory Committee on Cancer and Radiotherapy of the question of smoking and lung cancer.[1] The Committee was of the opinion that:

"1. There is a relationship between smoking and cancer of the lung."

Although saying that there is strong presumptive evidence that the relationship is causal, the Committee felt obliged to concede that the presence of a carcinogen for lung in tobacco smoke is not yet certain; that there is statistical evidence that the increased incidence of cancer of the lung is not entirely due to increases in smoking; and that atmospheric pollution and occupational risks might be operating.

These statements are in accord with the thinking of numerous active investigators in this country. They, too, want to know the relative importance of atmospheric pollution, smoking, and occupational risks in the causation of lung cancer. They also want to know specifically what the responsible agents are and the intermediate steps in lung carcinogenesis.

To this end, activity in research on mechanisms of action of agents involved in the pathogenesis of lung cancer has rapidly accelerated in recent years. The American Cancer Society has implemented many studies that have been undertaken in this direction.

Pathogenetic Factors

Some etiological factors in the production of lung cancer start outside the body. Others may be inherent in the cell. The epidemiological and biological evidence against a number of agents that have been incriminated as etiological factors is discussed in the accompanying article by Hammond. For purposes of this discussion, pathogenetic factors will be arbitrarily defined as the interaction of two or more factors contributing to the development of lung cancer. They will be called cofactors. The substances involved in such a cofactor relationship have been considered to have either additive or synergistic, augmenting or inhibiting, initiating or promoting action. They may be specific or nonspecific, direct or indirect, of intrinsic or extrinsic origin. While this problem is common to other forms of cancer, there is insufficient evidence to assume that what applies to one form would also apply to another. Therefore cofactor relationships specifically in lung cancer warrant examination.

External Factor(s). In a given case of lung cancer, it is not known whether one or more than one external agent is etiologically responsible. Numerous potential cofactors have been considered. Any or several of a host of irritants could prepare the epithelial soil for subsequent action of a carcinogen, whether in tobacco smoke, the inhaled atmosphere, or as a natural metabolite of the organism. A combined effect of two such substances might fit much of the observed epidemiological data. Alternatively, carcinogens may initiate, and cocarcinogens complete, the process.

For example, the compounds that have been reported to be present in tobacco smoke include aldehydes, ketones, acids, alcohols, alkaloids, other nitrogen compounds, hydrocarbons, inorganic compounds, and others.[27] Any one or several of the numerous compounds represented in these chemical classes could act as a cofactor. The substances range from those

soluble only in water to those soluble only in organic solvents. Many carcinogens have greatest solubility in organic solvents. The idea has been entertained that carcinogenic components of tobacco-smoke condensate may be carried into cells by virtue of their ability to dissolve in other constituents that, in turn, are soluble in body fluids. The substances acting as solvents then would serve in a cofactor capacity.

The suggestion has been made that no single substance in tobacco smoke is present in sufficient concentration to be carcinogenic. A combination of such a carcinogen and a cofactor might be sufficient for carcinogenesis. Only the most cursory studies along these lines have been carried out.

Funnelling into the larger bronchi of foreign material caught in outdrifting mucus may act as a mechanical cofactor.[32] Here the efficiency of ciliary action may be critical. Components of smoke that inhibit ciliary action may play an ancillary role in slowing the removal of exogenous material from the tracheobronchial tree. Ciliary action is also affected by particle size and density. The distribution through the lung and potential carcinogenicity of inhaled particulates are also affected by their characteristics. If carcinogens are adsorbed on soot, carcinogenicity is decreased.[14]

Additive vs. Synergistic Cofactors. Aside from the additive or synergistic carcinogenic effects of two or more agents in tobacco smoke, the idea of synergism between tobacco smoke and atmospheric or other pollutants has caused speculation. Some believe that, regardless of the presence of small amounts of carcinogen in tobacco-smoke condensate, its major role is as a cofactor. Gellhorn's studies[16] on skin carcinogens suggest such a role. With smoking a cofactor essential for the action of carcinogens of smog, lung cancer would be expected to occur earlier or with more than additive frequency in the presence of both smoking and exposure to atmospheric pollution. The study of Stocks and Campbell[47] suggests that (1) lung cancer occurs among smokers with negligible exposure to air pollution, (2) it occurs among nonsmoking residents of a heavily air-polluted urban area, and (3) its incidence is roughly additive for those exposed to both. For example, among men 65 to 74 years of age, the death rate was 336 in 100,000 for nonsmokers in Liverpool, and for heavy smokers in the clean air of a rural part of Wales it was 506 per 100,000. The heavy smokers in Liverpool had a rate of 588 or 254 per 100,000 less than the sum of these rates, which was 842. The same held true for the combined groups, 45 to 74 years. The figures are consistent with the theory that cigarette smoking and exposure to atmospheric pollutants are not synergistic.

Specificity vs. Nonspecificity. While carcinogens have often been found to be more or less specific for certain tissues as well as for certain strains or species of animals, the property of carcinogenicity of both tobacco tar[5, 16, 43, 51, 52, 53, 54] and smog [5, 13, 28] for systems other than human lung is of more than casual interest to several investigators. The criticism has frequently been made that such data may not be applicable to man.[41] Similar arguments have been advanced for carcinogenicity in organ systems other than the lung. When demonstrated for two or three other species, carcinogenicity for man becomes more likely. The same reasoning is used with respect to specificity of a carcinogen for different organ systems.

Although tobacco-smoke condensates have been shown to be carcinogenic for lung,[43] skin,[5, 43, 51, 53] and bladder[24] in at least three strains of mice[50] and rabbits,[17] to date these findings have been achieved with highly complex mixtures; there is no proof that the active agent is the same compound in each instance.

Direct or Indirect Cofactor. By indirect cofactor is meant one that acts through an intermediate step rather than by enhancing the mode of action of a carcinogen. Its action may therefore be that of a precursor. It may either increase or decrease the susceptibility of cells to a carcinogen. For example, under such a cofactor relationship would be included a history of any exposure or disease leading

to proliferative changes in the bronchial epithelium.

After the influenza pandemic of 1917–1918, Winternitz[19] called attention to proliferative alveolar epithelium and suggested that this might predispose to the development of cancer. Subsequently Niskanen[38] saw metaplastic bronchial epithelium frequently in cases of chronic bronchitis, bronchiectasis, and tuberculosis but not with malignant transformation. In a discussion of the pathogenesis of bronchial carcinoma, Rennie[42] discounted any association with tuberculosis, silicosis, bronchiectasis, bronchitis, emphysema, or any chronic lung diseases resulting from exposure to war gases.

On the other hand, an extensive study of 1267 World War I prisoners poisoned by mustard gas was made by Case and Lea[6] to determine the incidence of lung cancer. A significantly increased number of deaths from cancer of the lung was found in the exposed group, as well as in a bronchitis group that had not been exposed. Unfortunately, no smoking or residential history was obtained for the men, and the control group was composed of single-leg amputees. Their smoking habits may well have differed from the others. Palmer[39] had previously reported that, by history, clinical evidence, and radiological evidence, bronchitis is more common in heavy smokers than in light smokers or in nonsmokers.

Metaplasia and Precancer. The question of whether metaplastic changes are precursors of carcinomas in situ is a critical one.

Several studies correlating tissue changes with cancer of the respiratory tract are available. Moore and others[36, 37] observed a large amount of leukoplakia in habitual tobacco chewers, which they felt would have progressed with further stimulation into "frank malignancies." They found the association between the use of snuff and chewing tobacco and cancers of the mouth was statistically significant. Friedell and Rosenthal[15] felt that the patients with the greatest leukoplakic reaction were the ones who most often developed cancer at that site.

Mellors[35] was able to localize fluorescent material from cigarette smoke within squamous epithelial cells scraped from smokers' buccal mucosa. Nonsmokers had no fluorescent material in their smears. He also found that the fluorescent material has a predilection for keratohyalin granules commonly seen in leukoplakia.

Ryan and others[44] made a study of the pathological effects of smoking on the larynx and found significantly greater thickness of epithelium in smokers than in nonsmokers.

Recently, Auerbach[2, 3] and his coworkers have examined sections from tracheobronchial trees obtained at autopsy by step sectioning and preparing 180 to 200 blocks of each tree. One or more slides from every block were examined by two pathologists. Basal-cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ were recorded without access to clinical information. Each parameter was found to increase in frequency of occurrence from those who had never smoked through those who smoked one or more packs of cigarettes per day. In those with lung cancer, all characteristics were more common than in the heavy smokers. Cancers were never seen in the absence of hyperplasia, metaplasia, and atypism.

With a different approach, Chang and Cowdry[8] and Chang[7] studied whole mounts of bronchial epithelium obtained at autopsy from a major bronchus of smokers and nonsmokers. In seventy-one cases, smokers, on the average, had shorter cilia, more numerous goblet cells, thicker epithelium, more metaplasia, more intraepithelial inflammatory cell infiltration, and more frequent carcinoma in situ.

While the actual transition between the metaplastic epithelium and neoplastic cells is difficult to demonstrate, Black and Ackerman[4] believe the initial stage in the formation of carcinoma in situ of the lung is progressive metaplasia of the surface epithelium with cellular hyperactivity in the basal layer.

Kuschner[29] has not seen experimental epidermoid cancer of the lung without neighboring metaplastic changes. Black

and Ackerman point out, however, that these associations may be coincidental, since similar metaplastic changes take place in bronchiectasis, lipoid pneumonia, tuberculosis, and chronic lung abscess, none of which is particularly associated with carcinoma of the lung. It is not yet known which, if any, of these acquired alterations in cytological structure of bronchial epithelium are necessary in the production of lung cancer.

Endogenous Factors. The question has often been asked why so many heavy smokers do not get lung cancer if cigarette smoke is an etiological factor. Few attempts to answer this have been made. Nonspecific susceptibility may be manifest by the metaplastic changes already discussed. In this case, an individual would not get lung cancer unless he had been exposed previously to agents giving rise to proliferative epithelial changes. There is insufficient evidence to support or deny this concept. On the other hand, specific susceptibility or resistance would depend on variations in the reaction of the host to either carcinogens or their cofactors. Maurer and Spain,[34] Harkavy,[20] and others feel that tobacco smoke produces hypersensitive reactions more commonly than is generally realized. Lowell[31] concedes that hypersensitivity to tobacco exists as manifest by dermatitis and respiratory allergies. Whether such sensitivity has import in carcinogenesis is, of course, not known.

It is of passing interest to know that Rapport[40] has found antigenic differences between normal tissue and tumor in specimens from human beings, most notably in lung. It would indeed be fortuitous if antigens found in lung cancers could be traced to substances that had been inhaled.

Antigens, being frequently formed by combination of substances of exogenous origin with body proteins, are receiving increasing attention by oncologists. Heidelberger[21] has demonstrated a good correlation between the protein-binding capacity of seven C^{14}-labelled hydrocarbons and their carcinogenic potency. Whether this is a causal or only a secondary correlation is not known, but evidence that protein binding is necessary for chemical carcinogenesis is growing.[21] Experimentally Shubik[46] has recently achieved protein binding of hydrocarbon in the lung.

Sex as a Cofactor. From epidemiological data[18] about 30 per cent of the difference between lung-cancer incidence in men and women remains unexplained after correction according to age and differences in smoking habits. Lilienfeld[30] has suggested that, since the lungs arise from a laryngeal anlage that develops secondary sex characteristics in adult life, such developmental differences may extend into the tracheobronchial tree and account for part of the sex difference in susceptibility to lung cancer. In support of the hypothesis that the sex difference of susceptibility to carcinogenesis is of endogenous origin, Lilienfeld found that abortions had occurred more frequently in women having cancers with a high male–female–incidence ratio (including those of lung and bronchus) than among women with other types of cancer. While the correlation could be secondary to a third exogenous factor, the possibility of an endocrine-determined predisposition of men to lung cancer can not be entirely dismissed.

Age in Pathogenesis of Lung Cancer. To say that age is a significant factor in susceptibility to lung cancer is of little help in explaining pathogenesis. Little is known of the morphological or cellular physiological changes of the lung occurring in adult life. Macklin, in a discussion of aging of the respiratory system, states there is a decline of efficiency of broncho-eliminative, nervous, and other functions related to respiration.[33] Although definite interstitial age changes occur, no metaplastic changes could be attributed solely to age. Woglom[50] in reviewing experimental tar cancer and Hueper[25] reviewing the evidence on chimney sweeps' cancer concluded that age per se is an unimportant factor. Others[9, 45] have found that, if anything, younger animals were more prone to develop induced skin and subcutaneous neoplasms than older animals. This is in contrast to incidence rates in

man and remains unexplained. Whether these findings apply in human lung cancer is a matter of speculation.

Dose and Latent Period. When all the facts are known a formula could theoretically be derived to indicate the relative contribution of the concentration of dose and time. One such formula states that the product of concentration, C, and time, T, must equal a constant for a given system before malignant transformation will take place. While this serves a useful purpose, it does not take into account the cofactors of endogenous and exogenous origin already discussed. Convincing data relating the age at onset of exposure to both concentration and time of exposure are not available. Discussions of latent period have dealt chiefly with intervals between beginning of exposure and diagnosis of cancer. How much of the interval is true latent period and how much is due to cumulative dosage effect is difficult to ascertain. The question is of more than academic interest. Latent period, used in the strict sense, connotes the irreversibility of a process that has already received its effective dose of carcinogen. On the other hand, cumulative exposures to subthreshold concentrations of carcinogens need not imply irreversibility, even though the total interval from beginning of exposure may exceed the latent period for a single dose in the same system.

Evidence of reversibility of cumulative doses on skin has been obtained for tobacco-smoke condensate by Graham and Croninger.[17] Epidemiological evidence from England and the United States is not completely consistent on this point. Doll[12] interprets his data as evidence that cessation of smoking among men who have smoked for fifteen or more years would not appreciably decrease their mortality rate from lung cancer. Hammond and Horn,[19] on the other hand, presented data, derived from their prospective study on the incidence of lung cancer, showing that men who had been regular cigarette smokers and stopped smoking at least a year prior to the study had lower lung-cancer–mortality rates than those who continued to smoke.

Discussion

In the scientific literature, controversy over the importance of cigarette smoking and atmospheric pollution in the causation of lung cancer has been limited. This is in contrast to statements emanating in the lay press in this country and abroad, as well as in correspondence and in a few editorials in medical journals. The existing differences of opinion hinge on what constitutes reasonable proof. No agreement has been achieved, and perhaps properly so, on what is required for reasonable proof of a causative factor in lung cancer. The question pertains as much to exposure to atmospheric pollutants as to cigarette smoking. If it is assumed that each may play a role, estimates of their relative importance in the total lung-cancer–death rate vary greatly.

To get at the question for any suspected etiological factor, two possible approaches are used. The pathogenetic approach takes two epidemiologically associated statistics and attempts to fill in the steps leading from one to the other, on the hypothesis that they are etiologically related. Some of the data bearing on this point have been covered in this review.

The other, or the direct method, entails a comparison of two matched populations, one exposed, and the other not exposed, to the suspected agent. In the case of human lung cancer, such a study would require a minimum of twenty years even if practicable. An alternative to this direct approach might be described as the withdrawal-type experiment in which a random half of a group of exposed individuals is withdrawn from exposure to the agent. It is noteworthy in this compromise measure that negative results would not be conclusive evidence that no etiological relationship exists. Withdrawal from further exposure during the latent period after a full carcinogenic dose would have no effect on mortality rates. As recently shown,[10, 26] the effective initiating dose may be extremely small provided there is subsequent exposure to cocarcinogens. In this case, removal of a population from carcinogens after chronic exposure with-

out withdrawing it from promoting agents may, for all practical purposes, be again altering the external relationships AFTER the pathogenetic process has become irreversible. However, as stated before, there is some epidemiological evidence, though preliminary, that withdrawal, at least from cigarette smoking, may decrease the mortality rate of lung cancer.

In the meantime, the physician must continually make clinical decisions on the best available, though often inadequate, information. Carl V. Weller, in the final chapter of his recent book on *Causal Factors in Cancer of the Lung*[48] summarizes the change in his own attitude as follows: "I have been resistant to a ready acceptance of the association between cigarette smoking and bronchogenic carcinoma. I have searched the literature for other reasonable explanations or for recognizable fallacies. I have found none of importance. As of today, I must agree with many of the specialists in statistical analysis and in the endemiology of cancer, that this association has been established."

References to articles mentioned are available upon request. Address:

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Correction

In the abstract, *Radiotherapeutic Progress* on page 38 of the March issue of CA:

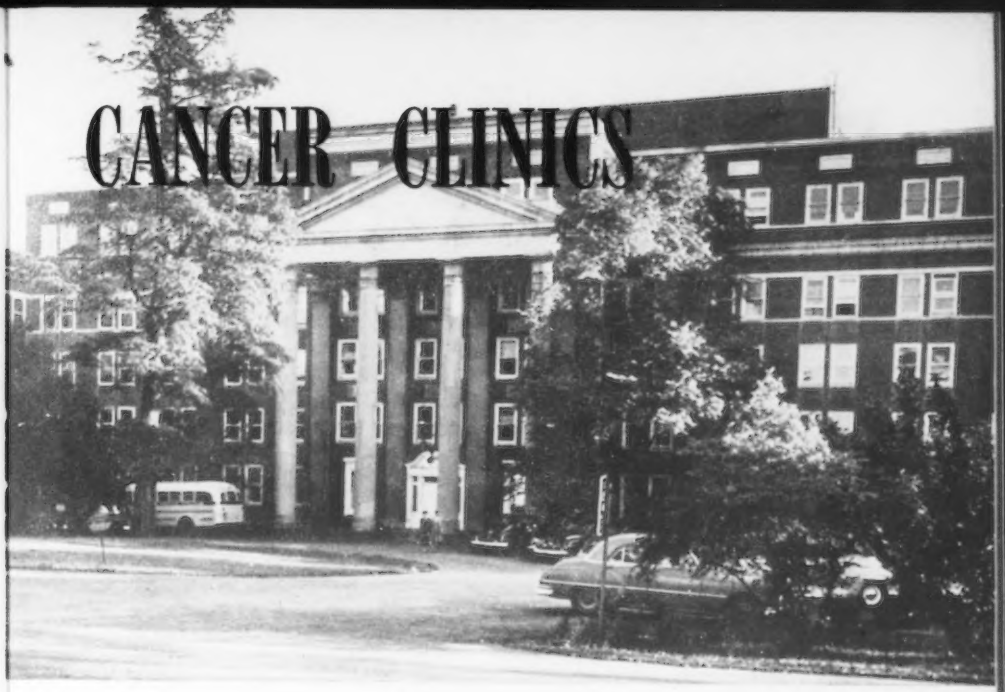
For *tumors*, in the fourth line, read *humans*.

For *Improvements . . .*, lines 10-14, read *With equal care and effort expended on treating the patients with conventional methods and less spectacular radiation equipment, results can be obtained comparable with those from the Big Berthas and atomic cannons.*

For (7) . . . *Wilms's tumor*, in the second column, read *(7) preoperatively in certain cancers such as breast with fixed axillary involvement, rectum with fixation, corpus uteri, bone, and some fixed kidney tumors, and postoperatively in stage II breast, thyroid, ovary, testis, Wilms's tumor of the kidney, carcinoma of the kidney with renal vein involvement or permeation through the capsule, and accessory nasal sinuses.*

For *melanosarcoma*, in the following sentence, read *melanocarcinoma.*

CANCER CLINICS



The Early Detection of Lung Cancer

Prepared by Katherine R. Boucot, M.D.

DR. BOUCOT: The increasing incidence of lung cancer makes early detection more important than ever. The fact that five-year–survival rates reported by surgeons continue to run less than 10 per cent clearly indicates the need for higher indexes of suspicion in the minds of the medical men who refer patients to surgeons, more prompt referral, and less delay in exploration. Until these physician delays are reduced to a minimum, pessimism over surgical results is unwarranted. It has been our experience, both in official mass surveys where routinely more than 100,000 Philadelphians a year are x-rayed and in the Philadelphia Pulmonary Neoplasm Research Project where 6139 men 45 years of age and older have enlisted for a ten-year semiannual x-ray and interview program, that the lay public is sufficiently interested in cancer to co-operate in every possible way. Less than one third of 224 consecutive survey-detected, proved lung-cancer patients had ignored symptoms except for reporting for chest x-rays.

There is no question but that those individuals who have x-ray abnormalities without symptoms have the best prognosis. In our experience, such persons usually have peripherally located tumors visible early radiologically because they are surrounded by ventilated lung.

DR. DAVID A. COOPER: It is my impression, too, that symptoms are likely to be present before x-ray changes in those cancers that arise centrally.

From the Woman's Medical College of Pennsylvania and the University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Dr. Cooper and Dr. Boucot are the responsible investigators of the Philadelphia Pulmonary Neoplasm Research Project.

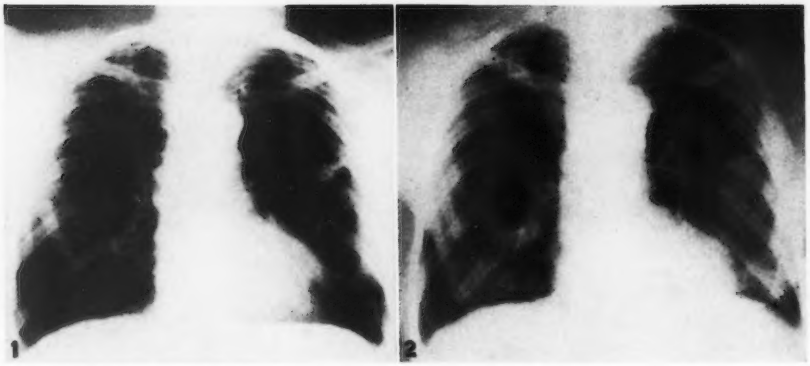


FIGURE 1. Case 1. B. C., a 62-year-old white foodhandler, had no symptoms. Photofluorogram on November 18, 1947, was erroneously interpreted as "negative."

FIGURE 2. Case 1. B. C. Photofluorogram on October 11, 1948, interpreted as abnormal, with infiltrations in the left mid-lung. No symptoms were present. Left pneumonectomy on November 24, 1948. Living and working eight years postoperatively.

DR. BOUCOT: Let us review the case of one of our Philadelphia foodhandlers, required by law to have annual chest x-rays.

Case 1

B.C., a 62-year-old, white foodhandler, required by Philadelphia law to report for annual chest x-rays, had his first on November 18, 1947 (Fig. 1), which was erroneously interpreted as negative. His second, on October 11, 1948 (Fig. 2), was recognized at once as abnormal. He was asymptomatic but, on being shown the two films, consented to hospitalization. Bronchoscopy and cytological studies of bronchial secretions were negative. However, because of the abnormal x-rays, exploration was performed on November 24, 1948, and left pneumonectomy was possible.

Mr. C. is living and working almost eight years postoperatively.

When I asked the radiologist who was reading the films at the time of the 1947 photofluorogram why he called this film "negative," he said he felt the abnormality in the left lung was either a pleural shadow or an old fibrotic scar of no current significance. This case dramatizes several important points. First of all, ANY abnormal shadow in a man more than 45 should be considered suspicious of neoplasm until proved otherwise. The characteristic x-ray appearance of lung cancer is the picture of advanced, hopeless disease. We are only now delineating the radiological appearance of curable lung cancer. Secondly, there is a tremendous variation in rate of tumor growth. This man has had a seven-year cure despite the fact that surgery was delayed for more than one year after an abnormal x-ray.

DR. COOPER: This foodhandler had no symptoms throughout the period of x-ray observation. Had there been delay while treating with antibiotics for "viral pneumonia," the outcome might have been quite different.

DR. BOUCOT: I agree completely! Such a history in men in the cancer age is like a dirge today. A significant percentage of our symptomatic cancer patients describe one or more such episodes. At the Western New York Chest Conference in Buffalo on June 28, 1956, the patient in one case presented had a pneumonia that responded dramatically to antibiotics. The negative x-ray after therapy gave false reassurance until too late.

DR. COOPER: Men more than 45 who have had pneumonia should be followed meticulously for several years. After all, we follow tuberculosis contacts and those

who have had "idiopathic" pleural effusions for at least five years to see if tuberculosis develops. Why not make it axiomatic that men older than 45 who have had pneumonia that has responded to therapy promptly so that the chest x-ray appears "negative" be followed every three months for one year, then semiannually?

DR. BOUCOT: I agree—though, now that the National Academy of Science has warned against an excessive lifetime body radiation, some may argue on that score. Most men more than 45 have established their families so that there need be no worry about effects on genes. If chest x-rays are properly exposed, there is very little exposure of the gonads, anyhow.

DR. COOPER: At this age, the possibility of the development of inoperable lung cancer outweighs the hypothetical radiation hazard. After all, Katharine, you and I, as ex-tuberculosis patients, have had considerably more exposure to radiation than we are suggesting for these men.

DR. BOUCOT: There is no question about that. Not only did I have chest x-rays every three months for more than twelve years, but I carried a right pneumothorax for the unconscionable length of nine and one-half years—during which I was fluoroscoped weekly!

DR. COOPER: What deleterious effects of radiation have you observed among your old pneumothorax patients?

DR. BOUCOT: None to my knowledge. Your experience in that area is larger than mine. What are your observations?

DR. COOPER: I know of no case of leukemia having developed in any of my pneumothorax patients. In fact, I have noted no harmful effects at all.

DR. BOUCOT: Let's return to another lung-cancer case. In this instance, the tumor was more centrally located than in case 1.

Case 2

B.S., a 65-year-old, white plasterer, had a negative chest x-ray on May 19, 1951 (Fig. 3), fifteen months before hemoptysis and seventeen months before the chest x-ray of October 11, 1952 (Fig. 4), that suggested advanced carcinoma. Yet this man was operable when hospitalized. He had a left pneumonectomy on November 25, 1952.

He is alive and working more than three years postoperatively.

Thus, rapid tumor growth associated with dramatic x-ray changes and symptoms need not mean inoperability.

DR. COOPER: Amen. The only real cures are among those resected and I refer such cases as emergencies to the surgeon

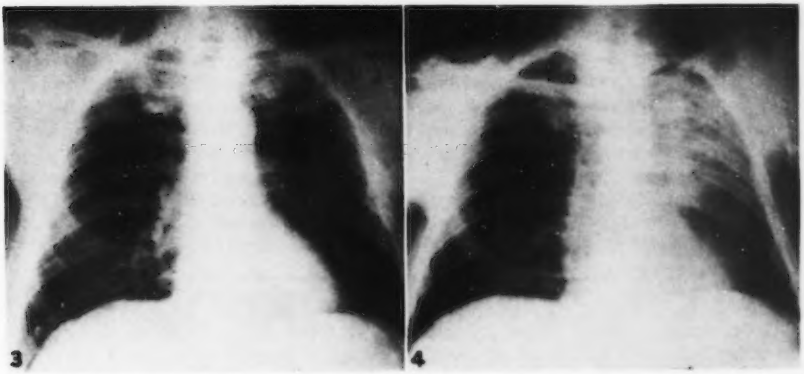


FIGURE 3. Case 2. B. S. Photofluorogram of May 19, 1951, revealed no abnormality.

FIGURE 4. Case 2. B. S. Photofluorogram of October 11, 1952, suggested advanced cancer. Left pneumonectomy on November 26, 1952. Living and working three years postoperatively.

TABLE 1

Proved Lung Cancer Analyzed by Hemoptysis and Smoking Habits

Type of smoking	With hemoptysis			Without hemoptysis		
	Total	With cancer		Total	With cancer	
		No.	%		No.	%
Nonsmokers	32	—	—	594	—	—
Cigarettes only	211	11	5.2	2,454	27	1.1
Occasional	37	1	2.7	396	2	0.5
Moderate	113	5	4.4	1,353	17	1.3
Heavy	61	5	8.2	705	8	1.1
Cigarettes and cigar/pipe	34	3	8.8	489	3	0.6
Cigars only	29	1	3.4	450	2	0.4
Pipe only	10	—	—	214	1	0.5
Cigars and pipe	8	1	*	173	—	—
Incomplete history	1	—	—	3	—	—
TOTAL	325	16	4.9	4,377	33	0.8

*Basic numbers too small for percentage estimation.

and let him decide about the inoperability.

DR. BOUCOT: Before we close, what about those whose chest x-rays appear negative?

DR. COOPER: All we have to offer such persons is semiannual chest x-rays—provided they have no symptoms.

DR. BOUCOT: That's true. It is well worth stressing the fact that, despite negative films, men in the cancer age group who have serious respiratory symptoms—hemoptysis, unilateral wheeze, worsening cough, etc., deserve meticulous clinical and radiological investigation, including at least bronchoscopy and bronchography.

DR. COOPER: We'll have more to say about that when the results of the Philadelphia Pulmonary Neoplasm Research Project are in. This research project has as its major objective a study of the chronological relationship between symptoms and x-ray changes in lung-cancer patients.

DR. BOUCOT: Already, in the follow-up period of seven to fifty-four months, we have had sixty-eight proved primary lung cancers. In nine instances these have developed after the initial visit to the Project. Seven of these patients have had symptoms before x-ray changes.

DR. COOPER: How many of the sixty-eight cases of cancer occurred in nonsmokers?

DR. BOUCOT: Only one so far. An analysis of proved lung cancer according to hemoptysis and smoking habits among the first 4702 men who entered the Philadelphia Pulmonary Neoplasm Research Project during its first three years (December 4, 1951, through December 3, 1954) is of interest (Table 1).

Really, the situation in regard to lung cancer today is grim but by no means hopeless. Semiannual x-rays in men more than 45 combined with careful further study for those with either respiratory symptoms or any x-ray abnormalities—particularly among heavy cigarette smokers—may well produce a higher yield of curable lung cancer.

"Governments . . . have so increasingly taxed cigarettes that now we all smoke them shorter and shorter to try to extract, certainly not our money's worth, but the utmost value possible. What an impasse now! All of us smoking ourselves to death to provide the money to treat us!"

Crawford, J. M.: [Correspondence.] Brit. M. J. 1: 1296-1297, June 2, 1956.

new developments in cancer

Breast Cancer Drugs . . .

Henry M. Lemon of Boston University has decided that cortisone plus thyroxin in small daily doses is as effective against advanced breast cancer as adrenalectomy or hypophysectomy. He found that, of forty patients treated with the hormones over the last three years, one third received no benefit, one third were helped up to six months, and one third improved substantially up to two years. Objective improvement included tumor regression, bone healing, disappearance of roentgen-ray shadows, and weight gain. Best results with drugs—or with surgery—have been seen in postmenopausal older, and castrate younger patients. Excretion studies indicate the drugs may act by suppressing pituitary function.

Gastric Ulcer, Gastric Cancer . . .

There's good news—and bad—for gastric ulcer patients in a study by Mark. A. Hayes of Yale University. The bad news: One in four stomach ulcers harbors a cancer. The good news: If surgical treatment is prompt, the cancers are highly curable. A review of ulcer complaints in New Haven between 1929 and 1949 disclosed a 25 per cent malignancy rate and showed further that five-year survival was experienced by 6 per cent of the cancer patients who postponed surgery for six months and 66 per cent of those who were operated upon within four weeks of symptoms.

Betatron Bombardment . . .

Preliminary results make the 22 Mev betatron look useful against stage-3 cancers of the uterine cervix. Gilbert H. Fletcher of M. D. Anderson Hospital, Houston, checked the two-year results of bombarding a broad pelvic area in seventy cases in which the disease had spread through the pelvis but apparently not beyond it. Three months after undergoing a seven-week radiation course, the patients were explored surgically for recurrence of cancer. Positive pelvic nodes were found in only 15 per cent. After conventional radiation, at least 50 per cent would prove positive.

Porphyrin Priming . . .

One year of clinical testing of porphyrins as an aid to radiation at the University of Minnesota has produced some promising results and a number of anomalies. Fifty patients, for the most part with various cancers, were primed intravenously with 500 mg. of porphyrins shortly before each irradiation three to six days a week. In about one half of them, the

porphyrins seemed to concentrate more or less preferentially in the tumors, potentiate the radiation effects, and afford a better remission than would radiation alone. In some cases, the porphyrin-radiation combination was used on one half of a tumor, while the other half was treated with radiation alone. In others with multiple tumors, some of the lesions would be given the combination, while the rest were merely irradiated. The results of this controlled experiment left little doubt in the minds of the investigators that in many cases porphyrin is a powerful roentgen-ray potentiator. Tumor regression was rapid and dramatic in some cases and long delayed in others—one woman discharged as having received no benefit from three weeks of treatment returned a few months later with the treated lesions well healed. One problem rests in obtaining a purified porphyrin. So far, each batch of porphyrin obtained has been chemically different and extremely inconsistent in its biological activity. There also is evidence that some of the impurities are much more active than the pure porphyrin, and investigators now are trying to identify the effective impurities. While immediate side effects were minimal in the dosages used: occasional tingling and infrequent and mild radiation sickness, a real problem has been posed by porphyrin's light-sensitizing properties. Patients treated with the fluorescent compound over a long period may remain light sensitive for months. They must be kept in a dark room during their period of treatment. Even brief exposure to sunlight can bring edema, blisters, and other severe sunburn effects. Among the many Minnesota investigators now working on the porphyrin problem are Samuel Schwartz, Karel Absolon, and Halvor Vermund.

Drug Screening . . .

Expensive in time, money, and scientific manpower are the present tedious methods by which compounds are screened for possible anticancer activity. To overcome this, David M. Greenberg and E. Norberg Sassenrath of the University of California have devised a simple, rapid method of determining how effective compounds are against specific tumors. They inject a known number of ascites-tumor cells into the bellies of mice and let them grow in both the drug-treated animals and untreated controls for a specific period. They then calculate the cancer's growth in six steps: (1) weigh the animal; (2) withdraw all fluid; (3) weigh the carcass; (4) subtract to give the amount of fluid; (5) spin down a specific small sample of the fluid and count the solid cells in the sediment; and (6) multiply the number of cells in the sample by its fraction of the entire volume. The ratio of tumor growth in treated and untreated animals is a mathematical expression of the effectiveness of the drug.

Radioactive Man . . .

Will the Atomic Age produce the Radioactive Man? Frank Queen of the University of Oregon and Ray Palmer of Richland, Washington, have found no undue radioactivity in the ashed bodies of fifty-two residents of the Lower Columbia River Area, which drains wastes from the enormous Hanford atomic-energy project. The average body in these examinations contained 0.00000000004 gm. of radon, which is about par for the species. Only one supercharged body was found. He was an elderly gentleman with six times the normal radioactivity; the pathologists speculate that he may have gone in for radium-water treatments in his younger days.

Cattle Eye Cancer . . .

Preliminary results indicate that costly cancer of the eye in cattle may be virus caused. Leon Dmochowski of Baylor and M. D. Anderson Hospital, Houston, has sighted suspicious particles in electron micrographs of the tumors.

effectiveness of the method, it is too early to tell whether the experiments have had clinical value. The Grahams are concerned with two other forms of resistance as well as antibody production -- the stimulation of histiocytes or macrophages and the development of epithelial areas believed to function against cancer and other antigenic entities. They have improved the anti-cancer epithelium development -- and enhanced radiation effects -- by using tumor vaccines and Freund's adjuvant.

Paul A. Younge (Harvard) was among several who offered evidence favoring conservative surgical management of cervical carcinoma in situ in young women desirous of having children. He gave the histories (8.58 years average follow-up) of seventy-three patients treated by: cauterization (fifty), conization (eleven), amputation of the cervix (five), polypectomy (one), and without treatment (six). Of the twenty-two conservatively or not at all treated, two had a hysterectomy six months and five years later respectively; and one of these, still alive and well eighteen years later, had developed invasive cancer. Of the seventy-three patients, seventy are still alive and well -- three have died of intercurrent disease after age 65, and one of these had been cured by cauterization as negative hysterectomy later showed. Carcinoma in situ persisted in seventeen of thirty-seven, and they were hysterectomized. The thirty-four patients who were not hysterectomized are alive and well. These results have persuaded Dr. Younge that the conservative approach is justified.

John G. Masterson (State U. Col. of Med., Brooklyn) reported that of twenty-six patients (mostly younger than 35 and wanting children), 60 per cent have been followed forty-eight months without progression of the cancer, 20 per cent have been treated surgically for invasive cancer, and 8 per cent with suggestive invasion also have been hysterectomized -- all of the latter two groups being well at this time. The fact that 20 per cent of these patients have borne children makes conservative treatment seem worth while.

Arthur Hertig (Harvard) said close observation should be made of cancer in situ cases and prompt action taken with any change in cell shape or size. He said cervical cancers are diseases primarily of married women, of married women who have borne children at an early age, more so in Negroes than non-Negroes, and to a much smaller degree in

Jewish than non-Jewish women. The average age of in situ cancer (in 200 hospital cases) was 38.7 years and of full-blown invasive cancer, 48 years. He considers in situ, as well as invasive, cancers irreversible.

H. R. Pratt-Thomas (Med. College of South Carolina) said that a paste made from whole human smegma and inserted several times weekly into the vaginal tracts of mice induced cervicovaginal cancers, sometimes in high percentages. Smegma contains cholesterol and various bacteria, including Mycobacterium smegmatus.

George N. Papanicolaou (Cornell) said that each of the four cell varieties normally found in the epithelium of the ectocervix and endocervix has a diagnostic and prognostic significance of its own and should be distinguished in smears. They include three squamous -- the superficial, intermediate, and parabasal -- and the endocervical cytological patterns.

Herbert E. Schmitz (Loyola, Chicago) asserted that supervoltage roentgen rays, high energy beams, and isotopes have enabled workers to raise five-year survivals in cancer of the cervix from 25 per cent to almost 50 per cent. In his practice radiation therapy is preferred to surgery in most cases. He uses a test dose of radiation and subsequent vaginal smears to determine whether the tumor is sensitive or resistant to radiation. He feels that with varied radiation and surgical methods, new hope can be held for many cases heretofore beyond salvage.

George V. Smith (Harvard) said that, while cervical cancer and pregnancy rarely are associated, a work-up of small experiences of many physicians indicates that patients treated early in pregnancy did much better than those treated near term or within four months of delivery.

Walter B. Quisenberry (Honolulu) reported that 322 physicians in Hawaii submitted 43,553 slides on 24,182 women to the Hawaii Cancer Society Vaginal Cytology Service during the last six years. Of the 141 cancers detected, sixty-three were asymptomatic and unsuspected. The average age of women with suspected cancer was 51 and with unsuspected cancer, 40. Sixty of the sixty-three with unsuspected cervical cancer are living and well, and three have been lost to follow-up. The physicians worked on this project without pay.

C. Bernard Brack (Hopkins) advanced figures to show that the cervical cure rate is not rising so rapidly as some

think. The salvage rate in one large series was 11 per cent higher in 1945 to 1949 than in 1940 to 1945. When corrections were made for a large increase in stage 0 and other early cases, however, the improvement could be laid completely to earlier detection, diagnosis, and treatment. In this series stage 0 was treated usually by surgery and clinical cases by radiation. Among other observations in this series: The younger the patient, the more advanced the tumor at diagnosis -- otherwise, age did not affect prognosis; Negroes were diagnosed later than non-Negroes -- but, under therapy, race doesn't affect prognosis; syphilitic patients had only a slightly lower survival rate than others; cell type did not affect prognosis.

Thomas H. Green, Jr., (Harvard and Mass. General) said that cancer of the vulva (commonest in the 50s, 60s, and 70s, but found from 30 to 102 years of age) usually responds well to surgical total removal of the organ and its lymphatic drainage. Inadequate treatment (partial removal, irradiation, or cauterization) can lower the five-year-survival rate as much as 50 per cent. In 200 patients observed over twenty-five years, the five-year -- survival rate was 47 per cent for those with lymph node involvement and 86 per cent for those without.

Albrecht Schmitt (Cologne) and Warren R. Lang (Jefferson) expressed satisfaction with colposcopy -- inspection under a bright light and 10x or greater magnification. It helps detect minor epithelial changes and indicates sites for biopsy.

Esther H. Dale, Osborne A. Brines, Gerald S. Wilson, and Harry M. Nelson (Detroit) reported finding 151 cervical cancers among 15,832 women -- 43 per cent primarily by smears and all confirmed by biopsy. They deplored the tendency to regard cervical cancer as almost exclusively a disease of older women -- more than one third of the patients were less than 40 years old.

BREAST

The breast sessions could be interpreted as demonstrating a growing respect for the techniques introduced by Edinburgh's Robert McWhirter -- simple mastectomy plus radiation. McWhirter himself was not at the conference, but if he had been he would have been surprised at the tolerance his often-abused beliefs received.

L. Henry Garland (Stanford) said: "It is believed

by some that radiotherapy combined with simple mastectomy is the best method of treatment of most cases of operable cancer of the breast. The absolute results obtained by its best-known proponents are better than those of any other comparable investigation to date." In his own small series of twenty-seven patients, Garland reported that fifteen have survived to the fifth year, with two of them having developed possible metastases and the remainder being "clinically cured." This compares favorably with others' experience with simple mastectomy and postoperative radiation: 43 per cent cures after five years and 25 per cent after ten. Radical mastectomy, with or without radiation, yields a 35 per cent five-year -- cure rate. He felt that simple mastectomy plus radiation is applicable to most patients with primary breast cancer, while radical mastectomy is useful only in patients with disease limited to the removable portions of the chest wall and axilla.

Ivor G. Williams (London) reviewed cases treated at St. Bartholomew's Hospital between 1930 and 1939 and concluded that "a program of careful conservative surgery and accurate radiotherapy is preferable for those with localized tumors, is possible in advanced cases, and, for those in between, the least harmful." For 329 cases treated with radical mastectomy, with or without radiotherapy, the respective five-, ten- and fifteen-year cure rates were 44 per cent, 27 per cent, and 17 per cent. For 216 cases given conservative surgery and radiotherapy, the rates were 46 per cent, 25 per cent and 22 per cent.

David V. Habif (Columbia U.) discussed the possibility that bacterial infection during or after surgery may be a mechanism of postoperative edema and reported that antibiotics have been highly successful in suppressing edema.

Ian Macdonald (U.S.C.) said that of every 100 women with breast cancer, twenty can be cured at any time up to three years after the disease starts, fifty-five are doomed because of inadequate bodily resistance and cancer's high growth potential, and some of the other twenty-five may be saved by early detection and treatment. "For the last twenty-five," he said, "the extent of their disease is a function of time. It is for this group that not only prompt but adequate, effective care may mean the difference between life and death. If it were possible to provide the most effective treatment now possible for all patients with a

minimum period of delay (one month or less), the maximum theoretical curability rate would be 45 per cent." He speculated that unknown biological factors determine the outcome of the invaded-invader struggle in the preclinical phase of breast cancer and that these factors are more important than the size of the tumor or the time or type of treatment. "This does not mean, however, that reasonably prompt, effective treatment is without importance to the woman with cancer of the breast, both for curative and relief purposes," he added. There was disagreement with some of these views.

A thoughtful and comprehensive review of steroid therapy and an equally extensive scientific exhibit on the subject were offered by Albert Segaloff (Tulane and Alton Ochsner Foundation). He urged generally cautious therapy with considerable attention paid to the stage and type of disease, age of the patient, urinary excretion patterns, and chemical and bio-assay procedures. He recommended castration for many premenopausal patients. One half his patients showed objective regression after surgical castration, but he declared the reason for these benefits is still a biological mystery. He himself did not ascribe it to estrogen-dependence of the tumors. He opposed radical mastectomy unless by itself it can be expected to effect a substantial cure rate. Testosterone can produce regression in about one of four patients, he said, with both osseous and soft-tissue metastases sometimes responding. Estrogens, he pointed out, afford benefits only in women five or more years past the menopause, and with them soft-tissue metastases respond better than osseous lesions. As for adrenalectomy and hypophysectomy, they "should be carried out only in those centers where large numbers of patients are available and where facilities for study are also available, so that the actual role of these procedures in the management of advanced breast cancer can be assessed."

PROSTATE

L. M. Franks (Imperial Cancer Research Fund, London) reported that prostatic cancers may invade the capsule, lymphatics, and blood vessels while still very small. A large percentage of clinical cases in those more than age 80, on the other hand, have no metastases, although some infiltration may be found. He said that there is no reliable method of distinguishing latent from active carcinomas. He

suggested that latency and arrest may involve some hormonal factor associated with aging.

William Fishman (Tufts), reporting on tests of ninety-one proved prostatic cancers and 1175 persons without the disease, said the Fishman-Lerner acid phosphatase--detection method registered 87 per cent of the untreated and 81 per cent of the treated cases. In Fishman's hands this was the most accurate of several methods tested.

Willard E. Goodwin and Joseph J. Kaufman (Los Angeles) concluded that "the most useful tool for early diagnosis of prostatic cancer is the index finger of a capable examiner who is mindful of the disease." They found other methods confirmatory, with "the final and clinching point in the diagnosis formal open biopsy."

Perry B. Hudson (Columbia-Delafield) reported that, among 750 men more than 45 years old without symptoms, unsuspected prostatic carcinomas were found in 13 per cent.

CHEMOTHERAPY

Sidney Weinhouse (Institute for Cancer Research, Philadelphia) inspired much favorable comment with a paper that outlined the problem of metabolism in cancer and the production of antimetabolites against cancer. His remarks tended to refute some of Warburg's old and recently revived cancer concepts as a bit too simple. He traced the normal and abnormal conversions of glucose and fat and emphasized that, while quantitative differences exist, no distinctive qualitative difference yet has been found. He pointed out that isotope studies in 1949 had shown unequivocally that tumor cells can oxidize glucose to carbon dioxide and at rates comparable with normal tissues. "This now constitutes evidence most damaging to the Warburg hypothesis," he said, "and for this and other reasons it does not seem likely now that an impairment of oxygen consumption is a feature of cancer tissue. This, of course, leaves the reason for the high lactic acid production still unsettled." He took the view that the breakdown of sugar to pyruvic acid may be so rapid that the normal oxidative channels are unable to cope with the flood of pyruvic acid, "and the only recourse is to be converted to lactic acid." He felt that this and other quantitative differences offer targets for chemotherapeutic attack. With only the major metabolic routes so far charted, and "behind them lying a vast virgin area awaiting biochemi-

cal exploration . . . one can not help being hopeful that the swift, well-nigh explosive progress in biochemistry is leading us to the goal which motivates all researchers in this field."

Roy Hertz (N.C.I.) reported that a drug, amphenone, has been used to suppress adrenal function and may help breast cancer cases in which adrenalectomy is indicated. It has some bad side effects, but less toxic derivatives are being sought.

MISCELLANEOUS

Henry J. Woloshin (Temple) warned against overlooking cancer in the small bowel. These cancers are infrequent but important. He said that in a survey of 81,000 surgical specimens collected at Temple in the course of twenty years, twenty-nine small-bowel tumors were found, twenty-six of them cancer. He said that routine gastrointestinal investigation usually stops with the stomach and duodenum, and cancer lower down may be missed.

H. B. Elkins and W. C. Keetel (State U. of Iowa) showed that ovarian cancer frequently can be found in the abdominal cavity when the disease appears localized to the ovary and this accounts for the deplorably high recurrence of ovarian cancer. They have used radioactive gold during their operation to kill the stray cancer cells, much as Rubin H. Flocks has used it to capture cancer seeds escaping from the prostatic area.

Stuart W. Arhelger (U. of Minn.) said that 25 per cent of patients with residual colic cancer now have been converted to negative by multiple operations in the "second look" program. Occasional success has been achieved in gastric cancers also by this program, which calls for reopening the patient six months postoperatively to seek out the cells left behind after the operation. As many as six "looks" have been undertaken in some patients.

E. Cuyler Hammond (A.C.S.) said that about one third of all cancer patients now being "saved" (they will survive five or more years), as compared with one fourth fifteen years ago. Greatest increase in survival rates were recorded for cancers of the large intestine, rectum, cervix uteri, corpus uteri, prostate, and endocrine glands. Little or no improvement was seen in cancers of the stomach, lung, esophagus, ovary, and soft tissues. Survival rates have risen for females -- from 29 per cent in 1935-1940 to 38

per cent in 1947-1951 -- and less rapidly for males -- from 19 per cent to 25 per cent for the same period.

Michael B. Shimkin (N.C.I.) reviewed records of cancer-case survival and expressed some dissatisfaction with the adequacy of the data. He called for better registries, better follow-up of patients, better criteria of diagnosis, clinical staging, and other aspects. He asked for studies going beyond clinical data to indicate what is best for the cancer patient.

Walter B. Quisenberry (Honolulu) reported that stomach cancer is about twice as frequent in Japanese men in Hawaii as in men of other ethnic groups. He listed among the areas to be investigated dietary and nutritional factors, oral health, occupational history (especially exposure to chemicals), emotional factors, and hereditary influences.

Fred W. Stewart (Memorial-N. Y.) deplored attempts to de-emphasize the benefits of early cancer diagnosis. He called them "definitely harmful and unwarranted." He cited the fact that cures of retinoblastoma have risen from 6 per cent to 59 per cent as demonstrating the value of increased awareness and early detection. He said that the reason anyone dies of cancer of the cervix is "lack of application of method, from fault of society, patient, and physician." He asserted that one series with breast cancers less than 2 cm. in size without spread to nearby nodes had a 93 per cent five-year-survival chance (95 per cent is the probability for the over-all age group). The same chance applies to melanomas in which the lesion is less than 20 sq. mm.

Arthur W. Hilburg (N.C.I.) presented data from 101 major cancer operations that indicated that cancer recurrence may be due largely to cancer cells left in surgical wounds. He found tumor cells in wound washings in thirty-four cases and evidence for suspecting they existed in eighteen more. In sixteen of the thirty-four positive cases and six of the eighteen suspicious cases, cancer has recurred. He proposed prophylactic chemotherapy accompanying surgery.

H. Mason Morfit (U. of Colo.) cited eleven cases in which reconstructive surgery enabled patients with cancers of the larynx, upper esophagus, or pharynx to eat again. He found that polyethylene plastics, a fine pliable stainless steel mesh, or a vitallium mesh covered with a skin graft from another body area served the purpose well.

COMING MEDICAL MEETINGS

Date	Meeting	City	Place
1956			
Oct. 22-24	New York State Academy of General Practice	Buffalo, New York	Hotel Statler
Oct. 22-27	Postgraduate Assembly in Endocrinology and Metabolism	Houston, Texas	University of Texas
Oct. 26-27	Southwest Cancer Conference	Fort Worth, Texas	Hilton Hotel
Oct. 29-30	Scientific Session, Annual Meeting American Cancer Society, Inc. Subject: Endocrines and Cancer All physicians and medical students are cordially invited to attend	New York City	Park Sheraton Hotel
Nov. 7-8	Southeastern States Cancer Seminar	Jacksonville, Florida	George Washington Hotel
Nov. 9-10	Clinical Symposium on Management of Carcinoma of the Breast	Houston, Texas	University of Texas M. D. Anderson Hospital and Tumor Institute
Nov. 12-14	Association of American Medical Colleges	Colorado Springs, Colorado	Broadmoor Hotel
Nov. 27-30	American Medical Association Clinical Meeting	Seattle, Washington	Civic Auditorium
Nov. 28-30	American College of Cardiology Clinical Workshop Program	Pittsburgh	Hotel Webster Hall
Dec. 2-7	Radiological Society of North America	Chicago	
1957			
April 8-12	American College of Physicians	Boston	
April 12-14	American Association for Cancer Research	Chicago	
April 14-20	American Society for Experimental Pathology	Chicago	
April 14-20	American Society of Pharmacology and Experimental Therapeutics	Chicago	
April 25-29	Pan American Congress on Cancer Cytology	Miami Beach, Florida	Eden Roc Hotel
May 5-10	International Congress of Otolaryngology	Washington, D. C.	Hotel Statler
May 12-13	International Congress of International Society of Bronchoesophagology	Philadelphia	
July 7-14	International Society of Clinical Pathology	Brussels	
July 9-12	International Society of Geographical Pathology	Paris	

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